Message

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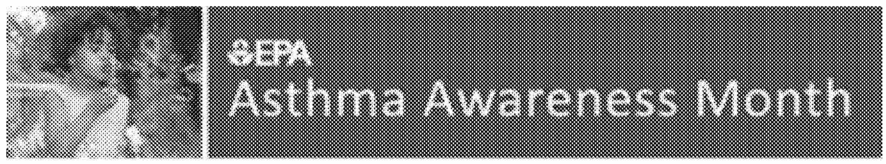
Subject: ORIA Weekly - The Week Ending May 18th, 2018
Attachments: ORIA Weekly May 18.docx

EPA United States Environmental Protection Agency

Office of Radiation and Indoor Air (ORIA)

ORIA Weekly – May 18th, 2018

May is:



RECENT EVENTS

NAREL Staff Participated in Career Extravaganza: On May 11, 2018, NAREL's Albert Smith, Nina Siddiqui, and Charmaine Tutson participated in Montgomery's Catoma Elementary School's Career Extravaganza. This event introduced students to career options that they may not be familiar with or don't know are available for them to pursue. NAREL demonstrated how to detect radiation in the environment by using different survey meters, showing how a reduction/oxidation reaction occurs using Glow Sticks, and how the pH of a solution affects a reaction. Albert, Nina, and Charmaine are pictured along with the students from Catoma Elementary School.

NCRFO Staff Participated in RadResponder Training and Exercise: On May 8-9, NCRFO personnel participated in a RadResponder training course provided at NCRFO's facility by representatives from Chainbridge Technologies. The course consisted of instructional presentations, hands-on practice, as well as an exercise that included the NCRFO Mobile Command Post, NCRFO field teams, field radiation surveys, and data upload and assessment using RadResponder.

RPD's Santillian Gave Actinide Geochemistry Presentation: On May 14-15, in Karlsruhe, Germany, RPD's Dr. Jay Santillan met with geochemical researchers at The Karlsruhe Institute of Technology (KIT-INE) to discuss issues related to actinide geochemistry. Dr. Santillan also gave a presentation on his work related to the Waste Isolation Pilot Plant (WIPP), and his current work on geochemical modeling using the Nuclear Energy Agency's Thermodynamic Database (TBD).

National Environmental Leadership in Asthma Management Award Winners Recognized: On May 9, the 2018 winners of the National Environmental Leadership Award in Asthma Management: the Community Asthma Prevention Program at Children's Hospital of Philadelphia and the Pediatric Asthma and Allergy Clinic at the Children's Health Center, Zuckerberg San Francisco General Hospital, were honored at a reception last week hosted by the Allergy and Asthma Network. After receiving their award, members of the winning programs participated in an informal learning session with OAR Deputy Assistant Administrator, Betsy Shaw. The winners shared details about their successful, comprehensive asthma management programs. The programs shared their challenges related to aged, urban housing and how that affects people with asthma. They also expressed how winning this prestigious award increases their program visibility and credibility.

Award Winner Photos
Top – Zuckerberg San Francisco General Hospital Award Winners: Dave Rowson, Kimberlee Honda, Silvia Raymundo, Christine Mayor, Betsy Shaw, Dr. Shonul Jain, Jon Edwards
Bottom – Children's Hospital of Philadelphia Award Winners: Dave Rowson, Charmane Braxton, Robin Miccio, Dr. Tyra Bryant-Stephens, Betsy Shaw, Michelle Jackson-Ware, Jon Edwards

RPD's Bacon (left), Matakas (right), Snead, and Wieder Attended National Alliance for Radiation Readiness (NARR) Conference – See 5/11/18 ORIA Weekly for more details.

- **NAREL Director Griggs Presented at West Coast Regional Radiation Response Meeting:** On May 9, 2018, in Washington State, NAREL's John Griggs gave a presentation at the West Coast Regional Radiation Response Conference on NAREL's radioanalytical capabilities and the training, guidance documents and rapid incident response methods NAREL has provided to state radiation laboratories over the past eight years. The conference was organized by the radiation laboratories from the states of California, Washington and Oregon and the Association of Public Health Laboratories. The conference focused on the laboratory response to a major radiological incident and the availability of federal laboratory assets to support states during an incident.

- **RPD's Schultheisz Met with South Korean Visitors:** On May 16, in Washington, DC, Dan Schultheisz of RPD met with a group from South Korea as part of the State Department International Visitor Leadership Program. The discussion generally covered EPA's radiation protection program and authorities, with emphasis on development of standards and guidance, emergency response, and monitoring (i.e., the national RadNet monitoring system). A representative from OAQPS also participated. The meeting was hosted by OITA.

- **RPD's Pawel and IED's Douglass Attended DOE Russian Health Studies Program Science Review Group Meeting:** On May 16, in Herndon, VA, RPD's David Pawel and IED's AAAS Fellow James Douglass attended the DOE Russian Health Studies Program Science Review Group meeting. Discussions included topics relating to the epidemiologic studies of health effects from low dose rate radiation exposure for nuclear workers of the Russian Mayak facility and residents of villages by the Techa River. Results from these studies are relevant to discussions on the use of linear, no-threshold (LNT) for radiation protection and risk assessment.

- **IED's Palmer presented proposed radon building code language at the Consensus Committee for the National Green Building Standard:** On May 15 and 16, IED proposed language for radon testing and system installation. The language was recommended and voted in favor by the main committee. The larger consensus body will vote on IEDs proposal after public comment later this year. If approved, adopters will earn points in the residential green rating system by demonstrating installation of radon-reducing features and testing the radon reduction system for effectiveness. Other IAQ measures were supported by IED and committee approved, such as 25 foot no-smoking around building perimeters.

- **IED's Tolbert Attended Conference on Health Disparities:** On May 16-19, in Philadelphia, PA, Elise Tolbert, a Fellow of the Association of Schools and Programs of Public Health (ASPPH), on assignment to IED, participated in the 11th Annual National Conference on Health Disparities. The conference theme was "Reducing Health Disparities Through Sustaining and Strengthening Healthy Communities."

- **IED's Enger Moderated Webinar on Improving Air Quality in Schools: HVAC Preventive Maintenance** – See 5/11/18 ORIA Weekly for more details.
- **IED's Palmer Presented Proposed Indoor Air Quality (IAQ) and Radon Code Language at the Consensus Committee for the National Green Building Standard (ICC/ASHRAE 700)** – See 5/11/18 ORIA Weekly for more details.
- **IED's Asthma Team Hosted a Webinar on Asthma In-Home Environmental Interventions** – See 5/11/18 ORIA Weekly for more details.
- **IED and NCRFO Staff Participated in the National Tribal Forum (NTF) on Air Quality** – See 5/11/18 ORIA Weekly for more details.
- **ORIA Staff Prepared for Upcoming ORIA Internal Drill Planning** – See 5/11/18 ORIA Weekly for more details.
- **RPD's Feltcorn Evaluated Requested Tier 1 Changes** – See 5/11/18 ORIA Weekly for more details.

RadNet Report for the Week of May 7th, 2018:

Overall monitor operational percentage is 89.9%. This is above the operational goal of 80%.

UPCOMING EVENTS (As of May 18th)

Radiation Protection and Emergency Response

- **ORIA Staff to Present at the Conference of Radiation Control Program Directors (CRCPD) Annual Meeting:** On May 21-24, in Charleston, SC, staff from across ORIA will be attending and presenting at the annual meeting of the state radiation control program directors. ORIA staff will attend committee meetings and are presenting on a number of topics including, an ORIA Overview (Jon Edwards, ORIA), Interactive Messaging Brainstorming (Jessica Wieder and Angela Shogren, RPD), Radiochemistry Capacity and Capability Collaboration Work Between ORIA's NAREL and ORD (Cynthia White, NAREL) Protective Action Guides Communication Tools (Stefanie Bacon, RPD), Technologically Enhanced Naturally Occurring Radioactive Material (TENORM) (Phil Egidi, RPD), Support to States and Tribes (Jeremy Johnson, NCRFO) and A Modular Approach to Radiation Field Operations Training (Kenneth Yale, NCRFO). NCRFO's Ed Wilds and RPD's Sara DeCair will also be in attendance.
- **RPD's Schultheisz to Represent EPA as Member of the U.S. Delegation of the Joint Convention on the Safety of Spent Fuel Management and the Safety of Radioactive Waste Management:** On May 21-25, in Vienna, Austria, RPD's Dan Schultheisz will represent EPA as a member of the U.S. delegation to the Sixth Review Meeting of the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management. The Joint Convention is a treaty-level agreement that requires preparation of a national report and presentation at the Review Meeting. The U.S. delegation will be led by the State Department and includes representatives from the Department of Energy and the Nuclear Regulatory Commission.

- **NAREL's Staff to Present at Radiobioassy & Radiochemical Measurements Conference (RRMC) 2018:** During the week of May 21st, in Portland, ME, NAREL's Keith McCroan will give workshop presentations on "The Performance-Based Approach to Data Quality" and "Standard Specification for Radiochemistry LIMS" at the 63rd annual RRMC. David Saunders will give a presentation on "Comparison of Visual Robust Fit to Traditional Commercial and Open Source Gamma Analysis Software". The RRMC provides a scientific forum for presenting and discussing topics on detecting, measuring, and analyzing radioactive materials, and offers a great opportunity for learning about the newest methods, instrumentation, and techniques available to radiation professionals and scientists. Also attending the conference are Shane Knockemus, Michelle Owens, Alison Tamasi, Charmaine Tutson and Erik Nielsen.

Indoor Environments Division

- **National Environmental Leadership in Asthma Management Award Winners to be Featured on Webinar:** On May 22, the 2018 winners of the National Environmental Leadership Award in Asthma Management, the Community Asthma Prevention Program at Children's Hospital of Philadelphia and the Pediatric Asthma and Allergy Clinic at the Children's Health Center, Zuckerberg San Francisco General Hospital, will be featured on an IED-sponsored webinar entitled, "Sustainable Strategies for Asthma Care: Best Practices From the 2018 Asthma Award Winners." These exceptional programs will share successful approaches for addressing asthma triggers, engaging community health workers and pursing program sustainability, methods to effectively track data to measure key program outcomes and cost savings, and strategies for pursuing reimbursement through Medicaid and from health plans. To date, over 400 participants are registered for this national learning webinar.

- **IED's Shimek and Curreri to Attend the 2018 National Coordinating Committee on School Health and Safety (NCCSHS) Meeting:** On May 23, in Rockville, MD, IED's Susie Shimek and Michele Curreri will participate in the annual NCCSHS meeting. Participants will strategize ways to address the effects of poverty on students, families and schools. Shimek and Curreri will present on how IED's resources, tools and guidance for schools can be included in strategies for addressing barriers to student achievement. More than 50 meeting attendees from private NGO's and public agencies working to promote health, safety and the academic success of America's children in our nation's schools will be in attendance.

To view previous editions of the ORIA Weekly, click here.

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Office of Radiation and Indoor Air (ORIA)
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RECENT EVENTS

NAREL Staff Participated in Career Extravaganza: On May 11, 2018, NAREL's Albert Smith, Nina Siddiqui, and Charmaine Tutson participated in Montgomery's Catoma Elementary School's Career Extravaganza. This event introduced students to career options that they may not be familiar with or don't know are available for them to pursue. NAREL demonstrated how to detect radiation in the environment by using different survey meters, showing how a reduction/oxidation reaction occurs using Glow Sticks, and how the pH of a solution affects a reaction. Albert, Nina, and Charmaine are pictured along with the students from Catoma Elementary School.

NCRFO Staff Participated in RadResponder Training and Exercise: On May 8-9, NCRFO personnel participated in a RadResponder training course provided at NCRFO's facility by representatives from Chainbridge Technologies. The course consisted of instructional presentations, hands-on practice, as well as an exercise that included the NCRFO Mobile Command Post, NCRFO field teams, field radiation surveys, and data upload and assessment using RadResponder.

RPD's Santillian Gave Actinide Geochemistry Presentation: On May 14-15, in Karlsruhe, Germany, RPD's Dr. Jay Santillan met with geochemical researchers at The Karlsruhe Institute of Technology (KIT-INE) to discuss issues related to actinide geochemistry. Dr. Santillan also gave a presentation on his work related to the Waste Isolation Pilot Plant (WIPP), and his current work on geochemical modeling using the Nuclear Energy Agency's Thermodynamic Database (TBD).

National Environmental Leadership in Asthma Management Award Winners Recognized: On May 9, the 2018 winners of the National Environmental Leadership Award in Asthma Management: the Community Asthma Prevention Program at Children's Hospital of Philadelphia and the Pediatric Asthma and Allergy Clinic at the Children's Health Center, Zuckerberg San Francisco General Hospital, were honored at a reception last week hosted by the Allergy and Asthma Network. After receiving their award, members of the winning programs participated in an informal learning session with OAR Deputy Assistant Administrator, Betsy Shaw. The winners shared details about their successful, comprehensive asthma management programs. The programs shared their challenges related to aged, urban housing and how that affects people with asthma. They also expressed how winning this prestigious award increases their program visibility and credibility.

Award Winner Photos

Top – Zuckerberg San Francisco General Hospital Award Winners: Dave Rowson, Kimberlee Honda, Silvia Raymundo, Christine Mayor, Betsy Shaw, Dr. Shonul Jain, Jon Edwards

Bottom – Children's Hospital of Philadelphia Award Winners: Dave Rowson, Charmane Braxton, Robin Miccio, Dr. Tyra Bryant-Stephens, Betsy Shaw, Michelle Jackson-Ware, Jon Edwards

RPD's Bacon (left), Matakas (right), Snead, and Wieder Attended National Alliance for Radiation Readiness (NARR) Conference – See 5/11/18 ORIA Weekly for more details.

- **NAREL Director Griggs Presented at West Coast Regional Radiation Response Meeting:** On May 9, 2018, in Washington State, NAREL's John Griggs gave a presentation at the West Coast Regional Radiation Response Conference on NAREL's radioanalytical capabilities and the training, guidance documents and rapid incident response methods NAREL has provided to state radiation laboratories over the past eight years. The conference was organized by the radiation laboratories from the states of California, Washington and Oregon and the Association of Public Health Laboratories. The conference focused on the laboratory response to a major radiological incident and the availability of federal laboratory assets to support states during an incident.

- **RPD's Schultheisz Met with South Korean Visitors:** On May 16, in Washington, DC, Dan Schultheisz of RPD met with a group from South Korea as part of the State Department International Visitor Leadership Program. The discussion generally covered EPA's radiation protection program and authorities, with emphasis on development of standards and guidance, emergency response, and monitoring (i.e., the national RadNet monitoring system). A representative from OAQPS also participated. The meeting was hosted by OITA.

- **RPD's Pawel and IED's Douglass Attended DOE Russian Health Studies Program Science Review Group Meeting:** On May 16, in Herndon, VA, RPD's David Pawel and IED's AAAS Fellow James Douglass attended the DOE Russian Health Studies Program Science Review Group meeting. Discussions included topics relating to the epidemiologic studies of health effects from low dose rate radiation exposure for nuclear workers of the Russian Mayak facility and residents of villages by the Techa River. Results from these studies are relevant to discussions on the use of linear, no-threshold (LNT) for radiation protection and risk assessment.

- **IED's Palmer presented proposed radon building code language at the Consensus Committee for the National Green Building Standard:** On May 15 and 16, IED proposed language for radon testing and system installation. The language was recommended and voted in favor by the main committee. The larger consensus body will vote on IEDs proposal after public comment later this year. If approved, adopters will earn points in the residential green rating system by demonstrating installation of radon-reducing features and testing the radon reduction system for effectiveness. Other IAQ measures were supported by IED and committee approved, such as 25 foot no-smoking around building perimeters.

- **IED's Tolbert Attended Conference on Health Disparities:** On May 16-19, in Philadelphia, PA, Elise Tolbert, a Fellow of the Association of Schools and Programs of Public Health (ASPPH), on assignment to IED, participated in the 11th Annual National Conference on Health Disparities. The conference theme was "Reducing Health Disparities Through Sustaining and Strengthening Healthy Communities."

- **IED's Enger Moderated Webinar on Improving Air Quality in Schools: HVAC Preventive Maintenance** – See 5/11/18 ORIA Weekly for more details.
- **IED's Palmer Presented Proposed Indoor Air Quality (IAQ) and Radon Code Language at the Consensus Committee for the National Green Building Standard (ICC/ASHRAE 700)** – See 5/11/18 ORIA Weekly for more details.
- **IED's Asthma Team Hosted a Webinar on Asthma In-Home Environmental Interventions** – See 5/11/18 ORIA Weekly for more details.
- **IED and NCRFO Staff Participated in the National Tribal Forum (NTF) on Air Quality** – See 5/11/18 ORIA Weekly for more details.
- **ORIA Staff Prepared for Upcoming ORIA Internal Drill Planning** – See 5/11/18 ORIA Weekly for more details.
- **RPD's Feltcorn Evaluated Requested Tier 1 Changes** – See 5/11/18 ORIA Weekly for more details.

RadNet Report for the Week of May 7th, 2018:

Overall monitor operational percentage is 89.9%. This is above the operational goal of 80%.

UPCOMING EVENTS (As of May 18th)

Radiation Protection and Emergency Response

- **ORIA Staff to Present at the Conference of Radiation Control Program Directors (CRCPD) Annual Meeting:** On May 21-24, in Charleston, SC, staff from across ORIA will be attending and presenting at the annual meeting of the state radiation control program directors. ORIA staff will attend committee meetings and are presenting on a number of topics including, an ORIA Overview (Jon Edwards, ORIA), Interactive Messaging Brainstorming (Jessica Wieder and Angela Shogren, RPD), Radiochemistry Capacity and Capability Collaboration Work Between ORIA's NAREL and ORD (Cynthia White, NAREL) Protective Action Guides Communication Tools (Stefanie Bacon, RPD), Technologically Enhanced Naturally Occurring Radioactive Material (TENORM) (Phil Egidi, RPD), Support to States and Tribes (Jeremy Johnson, NCRFO) and A Modular Approach to Radiation Field Operations Training (Kenneth Yale, NCRFO). NCRFO's Ed Wilds and RPD's Sara DeCair will also be in attendance.

- **RPD's Schultheisz to Represent EPA as Member of the U.S. Delegation of the Joint Convention on the Safety of Spent Fuel Management and the Safety of Radioactive Waste Management:** On May 21-25, in Vienna, Austria, RPD's Dan Schultheisz will represent EPA as a member of the U.S. delegation to the Sixth Review Meeting of the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management. The Joint Convention is a treaty-level agreement that requires preparation of a national report and presentation at the Review Meeting. The U.S. delegation will be led by the State Department and includes representatives from the Department of Energy and the Nuclear Regulatory Commission.

- **NAREL's Staff to Present at Radiobioassy & Radiochemical Measurements Conference (RRMC) 2018:** During the week of May 21st, in Portland, ME, NAREL's Keith McCroan will give workshop presentations on "The Performance-Based Approach to Data Quality" and "Standard Specification for Radiochemistry LIMS" at the 63rd annual RRMC. David Saunders will give a presentation on "Comparison of Visual Robust Fit to Traditional Commercial and Open Source Gamma Analysis Software". The RRMC provides a scientific forum for presenting and discussing topics on detecting, measuring, and analyzing radioactive materials, and offers a great opportunity for learning about the newest methods, instrumentation, and techniques available to radiation professionals and scientists. Also attending the conference are Shane Knockemus, Michelle Owens, Alison Tamasi, Charmaine Tutson and Erik Nielsen.

Indoor Environments Division

- **National Environmental Leadership in Asthma Management Award Winners to be Featured on Webinar:** On May 22, the 2018 winners of the National Environmental Leadership Award in Asthma Management, the Community Asthma Prevention Program at Children's Hospital of Philadelphia and the Pediatric Asthma and Allergy Clinic at the Children's Health Center, Zuckerberg San Francisco General Hospital, will be featured on an IED-sponsored webinar entitled, "Sustainable Strategies for Asthma Care: Best Practices From the 2018 Asthma Award Winners." These exceptional programs will share successful approaches for addressing asthma triggers, engaging community health workers and pursing program sustainability, methods to effectively track data to measure key program outcomes and cost savings, and strategies for pursuing reimbursement through Medicaid and from health plans. To date, over 400 participants are registered for this national learning webinar.

- **IED's Shimek and Curreri to Attend the 2018 National Coordinating Committee on School Health and Safety (NCCSHS) Meeting:** On May 23, in Rockville, MD, IED's Susie Shimek and Michele Curreri will participate in the annual NCCSHS meeting. Participants will strategize ways to address the effects of poverty on students, families and schools. Shimek and Curreri will present on how IED's resources, tools and guidance for schools can be included in strategies for addressing barriers to student achievement. More than 50 meeting attendees from private NGO's and public agencies working to promote health, safety and the academic success of America's children in our nation's schools will be in attendance.

To view previous editions of the ORIA Weekly, click here.

Rick White
U.S. Environmental Protection Agency
Office of Radiation and Indoor Air (ORIA)
(202)343-9335| white.rick@epa.gov

Message

From: McClintic, Howard [McClintH@ctc.com]
Sent: 2/15/2018 8:10:50 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]
Subject: Saving Hundreds of Millions of Taxpayers' Dollars Remediating Superfund Sites -- Get Rid of the LNT!
Attachments: FINAL LNT Presentation of Howard McClintic.pptx; Intro Email to EPA-LNT Project

Importance: High

CTC Foundation

Ensuring the Future Through Innovation, Science and Technology

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Good Day Mr. Wehrum:

Our mutual friend, Mark Bierbower, and I have discussed this Project countless times! My colleague, Dr. Robert (Bob) Golden, and I would like to schedule some time soon to have a Conference Call with you. We want you to clearly understand our Goals and Objectives as well as the importance and purpose of our soon to be completed peer-reviewed Science Committee Report.

Toward this end, I am attaching my PowerPoint Presentation. Bob and I each realize that slides 7 through 11 as being the most important because they visually depict the distortive effects of the LNT sharply contrasted with (and compared to) science-based data points. As you are aware, even now and through time, the former EPA Administrator, Gina McCarthy, consistently and emphatically repeats in interviews as well as in testimony over four years ago (on November 14, 2013), before the US House of Representatives Committee on Science, Space and Technology, she testified:

> "...Let me begin by stating that science is and has always been the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science upon which it relies. I firmly believe that environmental policies, decisions, guidance, and regulations that impact the lives of all Americans must be grounded, at a most fundamental level, in sound, high quality, transparent, science..."

(https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations

As you know, the Goal of this project is to determine, through a rigorous analyses of both the radiation and chemical data, the comparative validity of the science. The ***CTC Foundation's*** Science Committee that will compare and contrast the scientific evidence for the LNT and threshold models for radiation- and chemical-induced cancer and non-cancer effects in humans. This Committee was empaneled in October, 2016 and is comprised of recognized experts, from diverse disciplines and backgrounds. Their purpose is to develop a comprehensive peer-reviewed publication. Bob Golden and Dr. Edward Calabrese (https://www.umass.edu/sphhs/person/faculty/edward-j-calabrese) are Co-Chairs of the Science Committee.

We look forward to our Conference Call as soon as possible. We are very grateful for your time, attention and assistance – Thank You.

Most sincerely yours,

Howard

Howard G. McClintic

Executive Director

202 689 4586

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Eliminating the Linear No Threshold (LNT) Model for EPA Risk Assessment

Howard G. McClintic
Executive Director
CTC Foundation

Ensuring the Future Through Innovation, Science and Technology

Goals of This Presentation

- Describe and inform about the non-science based manner by which the US EPA relies on the LNT model for risk assessment of air- and waterborne chemicals
- Make apparent the exaggerated and unrealistic risks and benefits produced by reliance on the LNT for Clean Air Act-type regulations as well as for individual chemicals
- Briefly describe the scientific data which support threshold-based approaches for both chemicals and radiation
- Emphasize that our proposed Project is the only way that could lead to the elimination of the LNT for risk assessment and benefit/cost calculations

NAS Safe Drinking Water Committee (SDWC 1977)

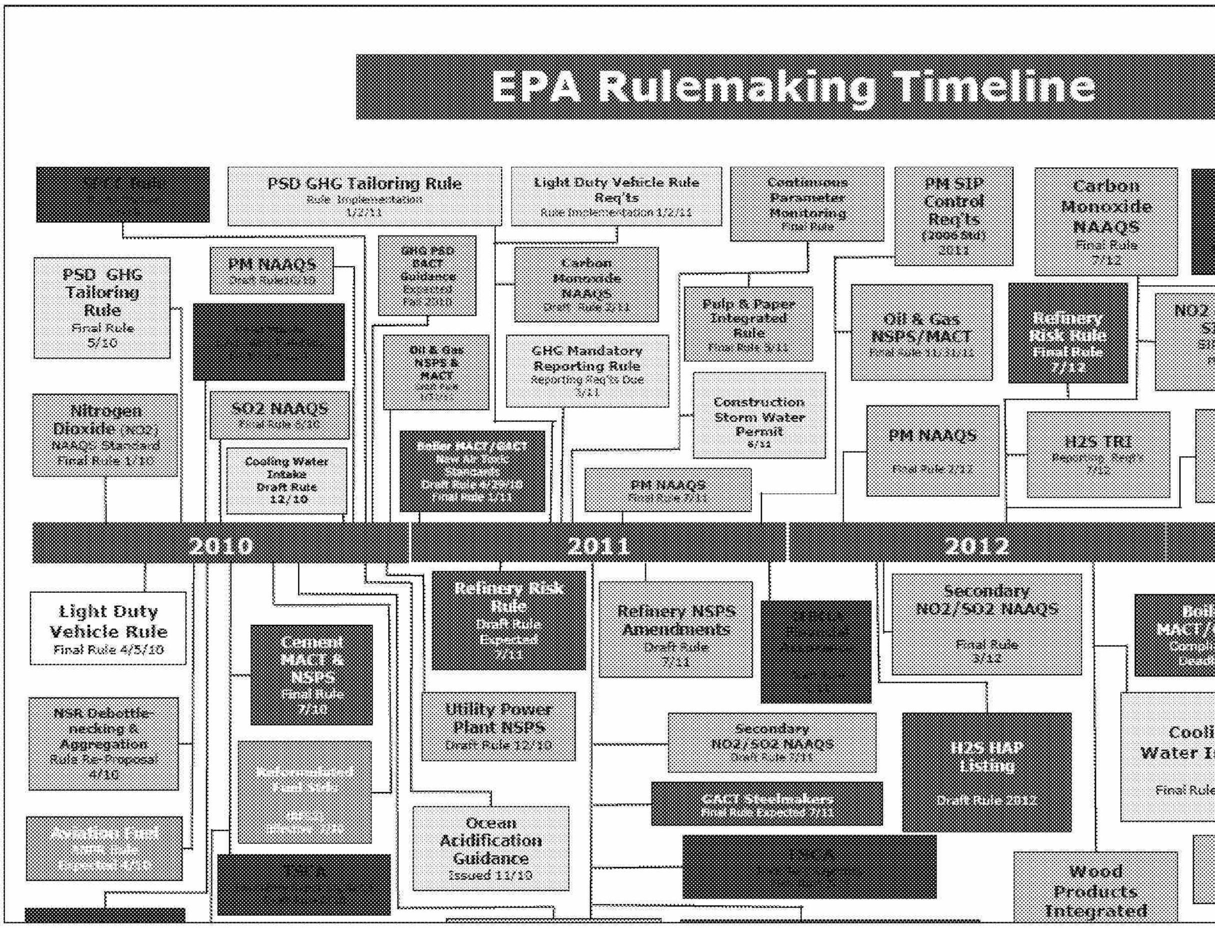
- Dr. Bob Golden worked on Vol. 1 of "*Drinking Water & Health*" (DW&H), developed for EPA as mandated by SDWA (1974).
- First time LNT model endorsed & used for chemical environmental cancer risk assessment.
- Foundationally based on radiation data for DNA mutation & cancer.

On-going Economic & Societal Consequences of LNT-Driven Regulations

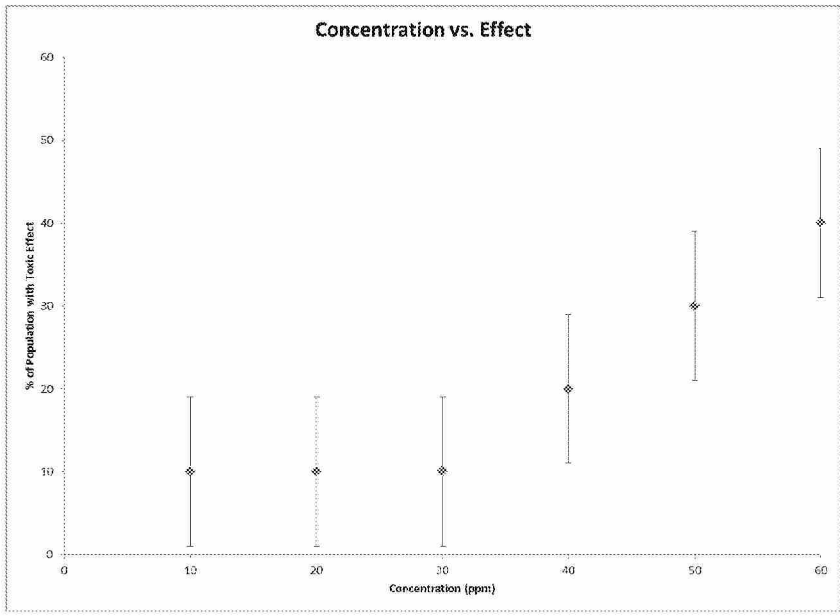
- Originally intended for exposure to radiation and cancer only; now used for chemical(s) and non-cancer risk assessment as well
- How virtually all potentially carcinogenic chemicals & radiation are regulated
- LNT plays substantial role in many regulations
- Many recent, on-going, and future EPA rulemakings have an LNT-driven component
- Staggering economic consequences and costs

The LNT is Involved in These Five Major Rulemakings Impacting the Power Sector

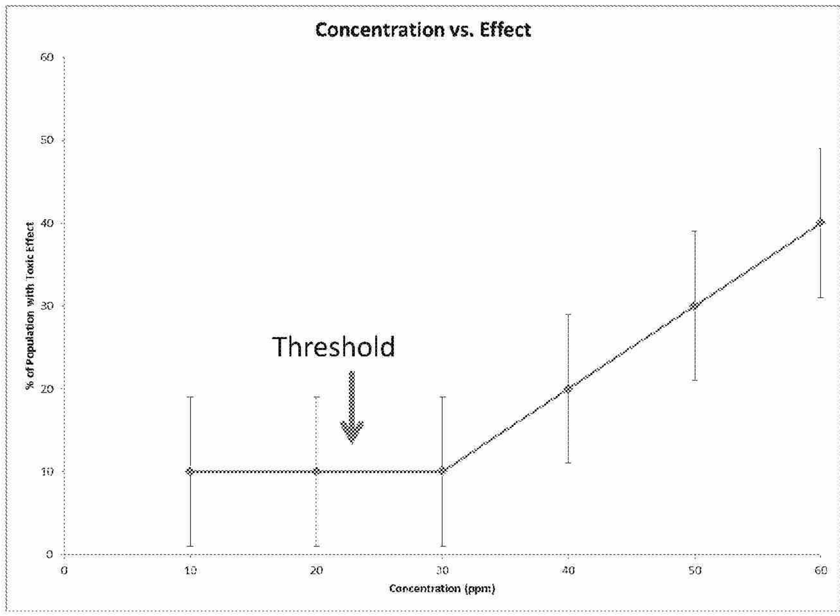
	Plants Affected	2013	2014	2015	2016	2017	2018	2019	2020+
SO_2 & NO_x (CAIR)	Existing+New			CAIR Replacement?					
Air Toxics (MATS)	Existing+New				Full Implementation				
Cooling Water Intake	Existing+New								
Coal Ash (CCR and ELG)	Existing+New								
Greenhouse Gas NSPS	New								


EPA Rulemaking Timeline
PSD GHG Tailoring Rule
Rule Implementation 1/2/11
Light Duty Vehicle Rule Req'ts
Rule Implementation 1/2/11
Continuous Parameter Monitoring
Final Rule
PM SIP Control Req'ts (2006 Std) 2011
Carbon Monoxide NAAQS
Final Rule 7/12
PSD GHG Tailoring Rule
Final Rule 5/10
PM NAAQS
Draft Rule 10/10
GHG PSD BACT Guidance
Expected Fall 2010
Carbon Monoxide NAAQS
Draft Rule 2/11
Pulp & Paper Integrated Rule
Final Rule 5/11
Oil & Gas NSPS/MACT
Final Rule 11/31/11
Refinery Risk Rule
Final Rule 7/12
Oil & Gas NSPS & MACT
GHG Mandatory Reporting Rule
Reporting Req'ts Due 3/11
Nitrogen Dioxide (NO2) NAAQS Standard
Final Rule 1/10
SO2 NAAQS
Final Rule 6/10
Construction Storm Water Permit
6/11
PM NAAQS
Final Rule 2/12
H2S TRI
Reporting Req'ts 7/12
Cooling Water Intake
Draft Rule 12/10
Boiler MACT/GACT
New Air Toxic Standards
Draft Rule 4/29/10
Final Rule 1/11
PM NAAQS
Final Rule 7/11
2010
2011
2012
Light Duty Vehicle Rule
Final Rule 4/5/10
Refinery Risk Rule
Draft Rule Expected 7/11
Refinery NSPS Amendments
Draft Rule 7/11
Secondary NO2/SO2 NAAQS
Final Rule 3/12
Cement MACT & NSPS
Final Rule 7/10
NSR Debottle-necking & Aggregation
Rule Re-Proposal 4/10
Utility Power Plant NSPS
Draft Rule 12/10
Secondary NO2/SO2 NAAQS
Draft Rule 7/11
H2S HAP Listing
Draft Rule 2012
Aviation Fuel
GACT Steelmakers
Final Rule Expected 7/11
Ocean Acidification Guidance
Issued 11/10
Wood Products Integrated

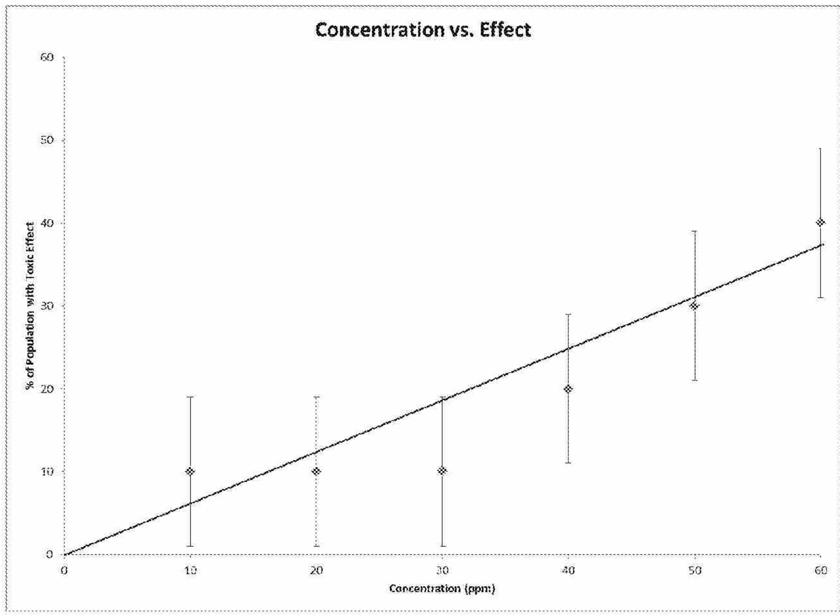
Typical Dose-Response Data Set



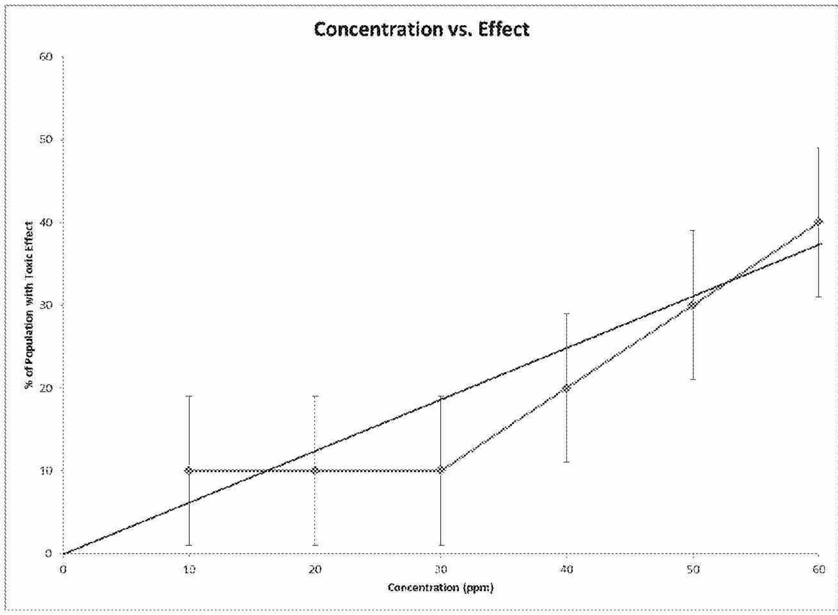
How a Biologist/Toxicologist Sees Data



How a Mathematician Sees Data

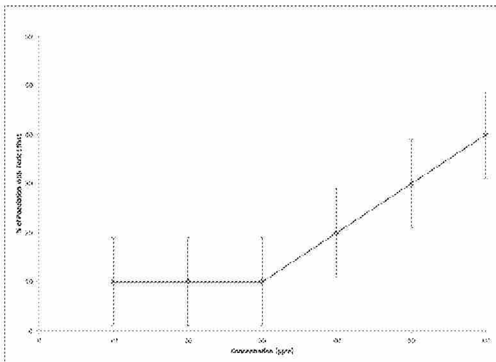


The Difference is Huge

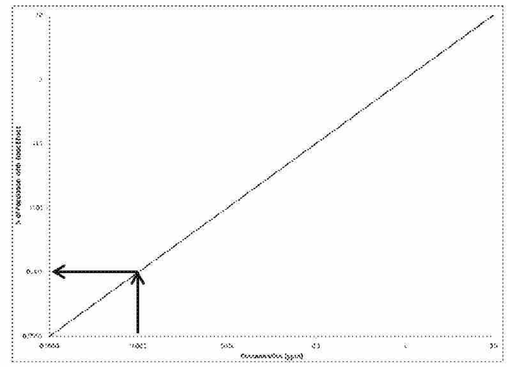


Comparison of Threshold to LNT

Threshold



LNT Model



30 ppm
0% of population (additional) =
0 cases of disease due to chemical

0.001 ppm
0.001% of population =
3150 cases of disease due to chemical

Effect on Regulations moving from Threshold to LNT

Chemicals of Concern

- Ozone
- $PM_{2.5}$
- Lead
- Mercury
- Sulfur dioxide (soon)
- Arsenic
- Formaldehyde
- Wave of the future – cumulative risk assessment

Why Continue to Use the LNT?

- Precautionary Principle
- In a large population, someone on the cusp of developing disease; any exposure will push them over the edge
- Policy or ideological decision, not scientific – no empirical evidence for LNT concept
- Made by policy makers (e.g., mathematicians & risk assessors; not toxicologists)

Specific Example, Using the LNT

- Mercury & Air Toxics Standard (MATS)
  - Lowered mercury emissions will prevent 0.00209 IQ point loss per child
  - 0.00209 IQ points x 244,468 children (USEPA estimates would benefit from rule)
  - 511 IQ points "saved" per year
  - 511 IQ points x $8k to $12K per IQ point decrease = $4.2M to $6.2M benefit from standard
  - IQ may vary as much as 3 to 4 points per child and may change over time or on retesting
  - Can't measure 0.00209 IQ point difference
  - Can't aggregate partial IQ points like money

Regulatory Implications of LNT Model

- EPA regulations now rely on LNT for non-cancer chemical effects
- EPA states, on numerous occasions, that chemical regulations are based on science alone (i.e., not policy); opens door for evaluating the science underlying the LNT.
- Recent regulatory actions rely on LNT to assess non-cancer health risks, e.g.,
  - Ozone & mercury based on the Clean Air Act (CAA), i.e., Mercury and Air Toxic Standards (MATS)
  - PM 2.5 regulations

Radiation Data

- Radiation-induced cancer risk still based on atomic bomb survivor data extrapolation (Biological Effects of Ionizing Radiation [NAS BEIR VII] report).
- Substantial data from DOE Low Dose Program (> 700 papers) on radiation-induced mutation & cancer show thresholds for these effects *in vivo*.
- Collective results from DOE (plus other data on radiation & chemicals) demonstrate the LNT:
  - Does not conform with newest experimental data using modern toxicological tools.
  - Is an "*artificial construct*" that needs replacement.

Chemical Data

- Since 1977 great strides in understanding how chemicals & radiation cause effects, e.g., toxicogenomics.
- NAS (2007) "*Toxicity Testing in the 21st Century*" called for new ways to test chemicals using human cells; thresholds obvious.
- Effects in key "adverse outcome" pathways can indicate potential adverse health effects; "computational toxicology"
- As long as LNT remains in place, new methods will never take their proper place in risk assessment

What Is The Social Cost of Carbon?

- As the LNT is NOT science-based, its use in economic benefit-cost analysis greatly exaggerates benefits.
- The federal government now assumes a ton of carbon-dioxide emitted in 2013 does roughly $36 in damage, rather than its previous estimate of $22, with the value rising each year
- A larger value for the social cost of carbon basically means that any standard or air-pollution regulation that reduces carbon-dioxide emissions will have higher benefits assigned to it.
- That could, in theory, make it easier for stricter standards to pass a cost-benefit analysis test

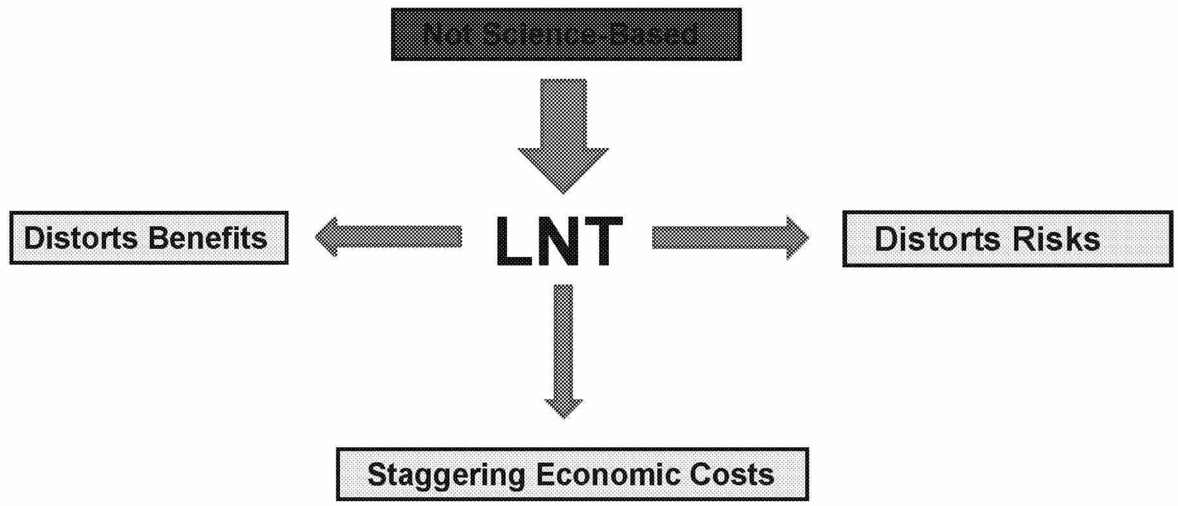
Conclusions (1 of 2)

- Adoption of LNT in 1977 questioned by historical radiation data plus new data for chemicals & radiation
- No empirical data supporting LNT
- Time is ripe for assessing the science of LNT vs. modern data for chemical or radiation risk assessment

Conclusions (2 of 2)

- Assertions that regulations are science-based opens door for assessing LNT science.
- Following sufficient analysis of underlying science, a different NAS committee should address risk assessment for chemicals & radiation without LNT component.

LNT "Facts"


Not Science-Based
Distorts Benefits
LNT
Distorts Risks
Staggering Economic Costs

LNT

Is There A Way Around the "Default" In the Road?

WHAT TO DO?

NOTHING = MORE OF THE SAME

- More regulations (NAM chart)
- CAA, MACT, SDWA, etc
- Individual chemicals(IRIS)
- Cumulative risk assessment
- More LNT-driven costs

CHALLENGE WITH SCIENCE

- Won' t be fast
- Won' t be easy
- Won' t be without controversy
- Will have major impact on regulations
- Fraction of LNT-driven costs to achieve

Path Forward

- Three-phased plan to "**ground-truth**" the science of the LNT model vs. threshold approaches
  - Multi-author peer reviewed analysis of relevant scientific data; emphasis on DOE Low Dose data
  - Multi-author peer reviewed economic analysis/case studies with/without LNT-driven "benefits" calculations
  - Advocacy/Communications/Public Outreach
- Congressional hearings

Path Forward

- Appropriations to fund joint DOD/DOE request for NAS to address non-LNT risk assessment approaches
- Widespread support for challenging LNT model
  - Numerous industry trade associations
  - Individual companies
  - State regulatory agencies
  - Animal rights organizations
  - House Energy & Commerce Committee

Contact Information

- Howard McClintic, Exec. Dir. ***CTC Foundation***, 202/689-4586; McClintH@ctc.com

- Robert Golden, PhD, ToxLogic LC, 301/977-9449; RGolden124@aol.com

Please call or e-mail if you would like to discuss or have additional information about our LNT Project

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Background Reading Material (1:4)

- **Edward J. Calabrese, Ph.D.**
  - Origin of the linearity no threshold (LNT) dose–response concept
  - How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response

- **Michael Honeycutt, Ph.D.**
  - Comments by Michael Honeycutt, Ph.D., with the Texas Commission on Environmental Quality Regarding the Primary National Ambient Air Quality Standards for Ozone and PM, and the Utility MACT http://science.house.gov/sites/republicans.science.house.gov/files/documents/hearings/100411_Honeycutt.pdf
  - The EPA's Pretense of Science: Regulating Phantom Risks, by Kathleen Hartnett White http://www.texaspolicy.com/sites/default/files/documents/epa-pretense-of-science-acee-kathleen-hartnett-white.pdf

Background Reading Material (2:4)

- New York Times Articles
  - E.P.A. Is Expected to Set Limits on Greenhouse Gas Emissions by New Power Plants
    http://www.nytimes.com/2013/09/14/us/epa-is-expected-to-set-limits-on-greenhouse-gas-emissions-by-new-power-plants.html?emc=edit_tnt_20130913&tntemail0=y&_r=0
  - An Unusual Public Battle Over an Energy Nomination
    http://www.nytimes.com/2013/09/16/business/energy-environment/a-federal-energy-nomination-sets-off-an-unusual-public-battle.html?hpw&_r=0
  - U.S. Coal Companies Scale Back Export Goals
    http://www.nytimes.com/2013/09/14/business/energy-environment/us-coal-companies-scale-back-export-goals.html?ref=business
  - China's Plan to Curb Air Pollution Sets Limits on Coal Use and Vehicles
    http://www.nytimes.com/2013/09/13/world/asia/china-releases-plan-to-reduce-air-pollution.html?ref=science
  - Challenges Await Plan to Reduce Emissions
    http://www.nytimes.com/2013/09/21/business/energy-environment/challenges-await-plan-to-reduce-emissions.html?_r=0

Background Reading Material (3:4)

- Greenhouse-Gas Fight Escalates: Administration's Higher Estimate for Cost of Carbon Raises Ire of Critics http://online.wsj.com/article/SB10001424127887324324404579040950076712782.html?mod=WSJ_hps_sections_news
- The 'Social Cost of Carbon' Gambit http://online.wsj.com/article/SB10001424127887323566804578551672709633396.html?mod=WSJ_Opinion_LEADTop
- Banning Demon Coal http://online.wsj.com/article/SB10001424052702303759604579095292685100308.html?mod=WSJ_Opinion_AboveLEFTTop
- An obscure new rule on microwaves can tell us a lot about Obama's climate policies http://www.washingtonpost.com/blogs/wonkblog/wp/2013/06/05/what-an-obscure-microwave-rule-says-about-obamas-climate-plans/

Other References

EPA Regulation of Greenhouse Gas Emissions from Existing Power Plants: Issues and Options http://www.vnf.com/news-alerts-854.html

Background Reading Material (4:4)

- EPA Proposes New Standards to Regulate Carbon Dioxide Emissions from New Power Plants http://www.vnf.com/news-alerts-878.html
- EPA Administrator McCarthy claims that their proposed rules are "science-based", which is "what" our Project challenges (http://www.c-spanvideo.org/program/315136-1)
- Climate Change Policy: What Do the Models Tell Us? Robert S. Pindyck. NBER Working Paper No. 19244. Issued in July 2013. NBER Program(s): EEE PE. www.nber.org/papers/w19244
- "Current State and Future Direction of Coal-fired Power in the Eastern Interconnection" http://www.naruc.org/Grants/Documents/ICF-EISPC_Coal-Whitepaper-071213_final.pdf
- Reassessing the Human Health Benefits from Cleaner Air http://www.cmpa.com/pdf/ReassessingCleanAirAug22.pdf

Goals of This Presentation

- ✓ Better informed about the non-science based manner by which the US EPA relies on the LNT model for risk assessment of air- and waterborne chemicals
- ✓ Made apparent the exaggerated and unrealistic risks and benefits produced by reliance on the LNT for Clean Air Act-type regulations as well as for individual chemicals
- ✓ Briefly described that there are scientific data that support threshold-based approaches for both chemicals and radiation
- ✓ Strongly emphasized that our proposed Project is the only way that could lead to the elimination of the LNT for risk assessment and benefit/cost calculations

Message

From: McClintic, Howard [McClintH@ctc.com]
Sent: 2/2/2018 4:02:58 PM
To: McClintic, Howard [McClintH@ctc.com]
Subject: Intro Email to EPA-LNT Project
Attachments: FINAL one page LNT project summary 1-23-17.docx

CTC Foundation

Ensuring the Future Through Innovation, Science and Technology

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Tax-Exempt Number: 25-1811888

Good Day,

My colleague, Dr. Robert (Bob) Golden and I are pleased to bring the important work of the ***CTC Foundation's*** Science Committee to your attention.

I am attaching a one page write-up of our Project that should provide the background that would be useful for a Conference Call that we would like to schedule with you at your convenience. Also, Bob put together this information summarizing the Science Committee's author, chapter title and status, which makes plain our progress.

Chapters	**Author**	**Status**
Prolog	Golden	Drafted
Introduction	Bus	In progress
History of LNT	Calabrese	Drafted
• LNT vs. threshold models: an evolutionary perspective	Costantini	Drafted
Why LNT needs to be abandoned of low-dose radiation risk assessment	Scott	Drafted
The impact of dose-rate on LNT hypothesis for radiation risk assessment	Brooks	Drafted
Thresholds for mutagenic carcinogens	Williams & Kobets	Drafted
Mechanistic aspects of chemical carcinogens demonstrating thresholds	H Clewell & R Clewell	In progress

Real world risks of chemical carcinogens assuming LNT is correct	Bus & Golden	To be drafted
Epidemiological analysis of low dose/dose rate radiation data	Ricci	Drafted
Economic implication of LNT vs. threshold models for benefit-cost analyses	Williams & Shamoun	To be drafted
Discussion & conclusions	All	To be drafted

Bob and I anticipate that you'll ask questions about this update and other matters during our conference call. Please suggest some dates and times for our Conference Call. We are grateful for your interest.

Many thanks, most sincerely yours,

Howard

Howard G. McClintic
Executive Director
202 689 4586

1-23-17
LNT Project Overview

Revisiting the Scientific Basis of the Linear No Threshold (LNT) Model as Contrasted with Threshold Models for Cancer Risk Assessment of Radiation and Chemicals

While science-based regulations are absolutely necessary to protect public health and safety, effective protection is not achieved by regulatory approaches that lack scientific merit. The single most distorting element of EPAs broad chemical regulatory agenda, including major regulations under the Clean Air Act (CAA) is the LNT model. The same holds true for regulations for the nuclear/radiation sector where the LNT model continues to be the default ignoring the abundant data and 1000s of papers documenting the adaptive and other mitigating effects of radiation. Even though the LNT model was originally adopted by the National Academy of Sciences (NAS) in 1956 for radiation and in 1977 for chemicals, it is now known that, even then, there were substantial data demonstrating that this model was scientifically invalid. Because LNT-driven regulations, whether for chemicals or radiation, are repeatedly claimed to be science-based, the underlying scientific foundation for such regulations, particularly the LNT model itself, should also, by definition, reflect empirical data. If such scientific data are lacking, as they are for the LNT model, science-based regulatory methodologies for both chemicals and radiation should be updated to reflect significant advancements in scientific knowledge.

The LNT Project, which is now well underway, will be conducted in two Phases. The first was the formation of a Science Committee, comprised of approximately ten individuals in the fields of toxicology, radiation biology, evolutionary biology, epidemiology, and economics. This Committee is in the process of preparing, as the sole deliverable, a comprehensive peer-reviewed publication[1] which will compare/contrast the scientific data supporting the LNT model with threshold models for chemical and radiation mutation and carcinogenesis. The focus of the Project will be to demonstrate that because there is no scientific support for the LNT model as contrasted with overwhelming modern data for threshold models such models should be the basis for regulations. Consequently, since EPA has repeatedly asserted that their regulations and models are based on "sound, high quality science," the goal of this effort is to use this as the basis for assessing the data for LNT and threshold models. With the progress achieved to date, the goal is to have the Committee's report completed and peer reviewed at the end of Q3 2017.

Following publication of the peer-reviewed report, the next Phase will be the formation of a Communications Committee. This group will generate interest/support for the development of risk assessment methodologies that are science-based and health protective, but do not rely on the LNT model. The ultimate goal would be for a Congressional hearing(s) and subsequent appropriations and funding for a new Committee at NAS (i.e., not BEIR)[2] to revoke its 1956 endorsement of the LNT and replace it with evidence-based cancer risk assessment approaches for chemicals and radiation without having to assume that the LNT model is scientifically valid. A paradigm shift of this magnitude will not be fast, easy or without controversy, but can only occur after the singular goal of this Project is achieved, i.e., convincingly demonstrating that compared to threshold models, the LNT model is scientifically invalid for purposes of radiation and chemical risk assessment as well as for economic benefit-cost analyses.

---

[1] A dedicated issue of Critical Reviews in Toxicology with full support from the editor.

[2] Based on a planning meeting at NAS in November 2015 for the anticipated Committee on the Biological Effects of Ionizing Radiation (BEIR VIII) it was clear the LNT would continue to be the default for radiation risk assessment.

Message

From:	Lewis, Josh [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B22D1D3BB3F84436A524F76AB6C79D7E-JOLEWIS]
Sent:	1/12/2018 1:59:40 PM
To:	Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
CC:	Wright, Rhonda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5d6d041a34ea466dac1f7985308e35ea-RWRIGH04]; Atkinson, Emily [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bb2155adef6a44aea9410741f0c01d27-Atkinson, Emily]; Millett, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c067caa6c93544f78c26ab08cc567d27-Millett, John]; DeLuca, Isabel [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b021c30cbee4637a7c7ca683e5e044a-IDELUCA]
Subject:	FW: One pagers for the oil and gas roundtable briefing books
Attachments:	ECOS-IOGCC Roundtable - Ozone Designations for 2015 Ozone NAAQS.docx; Roundtable backgrounder.Proposed Stays and NODAs.docx; Roundtable backgrounder.Proposed withdrawal of oil and gas CTG.docx; Roundtable Issue paper. NSPS reconsideration. 1.11.18.docx; Roundtable Issue Paper.TENORM.ORIA.1.11.18.docx

Bill – you'll recall Allison Davis mentioned these at the 5:15 meeting last night. We'll get these in both of your folders today.

These one-pagers are for the briefing books for all of the EPA attendees at the roundtable and they are based on publically available information.

For the roundtable itself, OAQPS was pretty clear that your presence there would be valuable, so we'll look to get you out to Denver on the afternoon/evening of Tuesday 1/23 so you're there for the 3 hours of the meeting on Wednesday. We'll also work some OAR-provided talking pts into Ken Wagner's opening remarks. We can talk more at 10:30 scheduling meeting.

Message

From: DeLuca, Isabel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0B021C30CBEE4637A7C7CA683E5E044A-IDELUCA]
Sent: 1/8/2018 7:55:47 PM
To: OAR Briefings [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2da922b09b7a4a18a19571005bff0297-OAR Briefin]
CC: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Lewis, Josh [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b22d1d3bb3f84436a524f76ab6c79d7e-JOLEWIS]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]; Dominguez, Alexander [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5ced433b4ef54171864ed98a36cb7a5f-Dominguez,]; Millett, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c067caa6c93544f78c26ab08cc567d27-Millett, John]
Subject: draft OAR web landing page
Attachments: Programs and Projects of the Office of Air and Radiation v1.docx

For Bill, Mandy, Clint, and Alex—

Here is a draft language for a potential landing page (web page) for OAR, to link into top OAR program areas. The links overlap somewhat with links on the “About OAR” web page, but this is shorter and would require less scrolling once laid out and formatted for the web.

If there’s time in tomorrow’s comms meeting, we could discuss messaging for the intro area of this page, and links/areas to add or drop.

Thanks,
Isabel

Isabel DeLuca
Office of Air and Radiation, US EPA
(202) 343-9247

Message

From: Edwards, Jonathan [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3715BC4DFC3E4D6CAF3AF1BF2FC5CA77-JEDWAR02]
Sent: 1/19/2018 7:26:04 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
CC: Lewis, Josh [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b22d1d3bb3f84436a524f76ab6c79d7e-JOLEWIS]
Subject: FW: APPROVED: Radiation social media messaging
Attachments: potential rad tweets jan 2018.docx

Bill and Mandy--- Just a quick FYI. As public concern has grown regarding North Korean nuclear capabilities, and the recent Hawaiian incoming missile false alarm, the White House / National Security Council has been pleased with EPA / ORIA's radiological emergency communications materials and has been turning to them for more public information. Please see attached. This is of course all being coordinated with OPA. ---Jon

From: Wieder, Jessica
Sent: Friday, January 19, 2018 1:01 PM
To: Millett, John <Millett.John@epa.gov>; Stevens, Katherine <stevens.katherine@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>; Matakas, Lauren <matakas.lauren@epa.gov>
Cc: Veal, Lee <Veal.Lee@epa.gov>; White, Rick <White.Rick@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Cherepy, Andrea <Cherepy.Andrea@epa.gov>
Subject: APPROVED: Radiation social media messaging

John, Kati and Nancy,

DHS Incident Comms just called and said we had White House approval, specifically from Vinnie Picard, to push public education on what to do in the case of a radiological emergency. (see exchange below)
Please see the attached drafted tweets that point people to our radiation protection webpages.

Any help on moving these forward would be much appreciated.

Jessica

Jessica Wieder
U.S. EPA
Radiation Protection Program
Center for Radiation Information and Outreach
w: 202-343-9201
c: 202-420-9353

message truncated

Message

From: Kenney, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6FF86939E44DA49D88840B2353F022-KENNEY, JAMES]
Sent: 1/18/2018 4:15:45 AM
To: Wagner, Kenneth [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=048236ab99bc4d5ea16c139b1b67719c-Wagner, Ken]; Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Benevento, Douglas [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93dba0f4f0fc41c091499009a2676f89-Benevento,]; Traylor, Patrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b6d06c6b766c4b4b8bfdf6b0fea4b998-Traylor, Pa]; Letendre, Daisy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b691cccca6264ae09df7054c7f1019cb-Letendre, D]; Idsal, Anne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b1beca8121fb47a08e82b6bf2247a79b-Idsal, Anne]; Beeler, Cindy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9b11e688258c462bab293a6df8ff4b27-Beeler, Cynthia]; Bohan, Suzanne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a83d74ccf7c4b40acdbf09c093f3b16-Bohan, Suzanne]; Chapman, Apple [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c52a18bcf6164b6d9f04545db694cac1-ACHAPMAN]; Mia, Marcia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6590c44762d64ce28ab3d7a7fbb14673-MMia]; Lawrence, Rob [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b22505b64aee401eba1a31e9b50f61d1-Lawrence, Rob]; Teichman, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=20074f3f79c444a4b324cfbb890c7f56-Teichman, Kevin]; Werntz, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=479307949d9f4864a47eba97f835b7fa-Werntz, Jim]; Cozzie, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ee8c3582a39d4d81ac38f29a2b3abb2d-DCOZZIE]; Werntz, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=479307949d9f4864a47eba97f835b7fa-Werntz, Jim]; Mclain, Jennifer [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2bc5b268184348bbb383a56b0042b603-Jennifer Mclain]
Subject: Roundtable Info for EPA Attendees
Attachments: Roundtable Briefing Paper (Internal Use Only).docx; Oil and Gas Roundtable Briefing Book (Internal Use Only).pdf; ONG Roundtable Comms (Final).docx

Importance: High

Hello EPA Colleagues,

You are receiving this email because you are a confirmed attendee of the Oil and Natural Gas Roundtable happening in Denver, Colorado next week. In addition to the materials shared with all participants this morning, I am now sharing **internal** EPA information with you. Attached to this email, please find:

(1) A two page briefing paper on the oil and natural gas roundtable. This paper provides background information, objectives, etc.

(2) A twenty-four page briefing book summarizing current oil and natural gas happenings around the U.S. which EPA has a role. The issues in the briefing book represent the likely issues stakeholders would bring to EPA's attention.

(3) A two page communications document with desk statements and assorted questions and answers.

You now have all the participant information I intended to share with you. If you have additional questions, please let me know.

I look forward to seeing you all next week!

Thanks,
Jim
~~
James C. Kenney
Senior Policy Advisor
Unconventional Oil and Gas
US EPA

Desk/Mobile: (202) 768-2618
Email: kenney.james@epa.gov

Please note: *I am geographically located in Albuquerque, New Mexico (Mountain Time Zone).*

Message

From: Shaw, Betsy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=31CA1476A7674825A131CB2C0D6C88C8-BSHAW03]
Sent: 11/20/2017 10:15:50 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]
Subject: OAR's proposed revisions to the EPA Strategic Plan
Attachments: EPA-HQ-OA-2017-0533-0002 - SP for Pub Comment_OAR Obj 1.1 revisions 11 2....docx; Summary of Comments on the Air Section of the Strategic Plan 11 20 17.docx

Hi Bill,

Per my mention at our morning meeting, attached (and soon to follow in your box) is a one pager that summarizes the comments received on the air section of EPA's Strategic Plan for FY2018 – FY2022 during the public comment period and a markup (see pp. 5 – 8) indicating edits we propose to make responding to the comments we believe we can address. We are supposed to submit our proposed revisions to OCFO by COB tomorrow. Let me know if you have any questions, concerns, or suggestions.

Thanks,

Betsy

Message

From: llwforuminc@aol.com [llwforuminc@aol.com]
Sent: 2/5/2019 3:45:34 PM
To: Llwforuminc@aol.com
Subject: LLW Forum News Flash: National Council on Radiation Protection and Measurements (NCRP) Releases Guidance for Radiation Protection in the United States

National Council on Radiation Protection and Measurements (NCRP)

NCRP Releases Guidance for Radiation Protection in the United States

On February 4, 2019, the National Council on Radiation Protection and Measurements (NCRP) announced the newest guidance for radiation protection in the United States with the publication of Report No. 180 titled, *Management of Exposure to Ionizing Radiation: Radiation Protection Guidance for the United States (2018).*

The report is intended to serve as a tool for those responsible for implementing radiation protection programs and developing regulations in the United States.

Interested stakeholders can purchase a copy of NCRP Report No. 180 at https://ncrponline.org/shop/reports/report-no-180-management-of-exposure-to-ionizing-radiation-radiation-protection-guidance-for-the-united-states-2018-2018/.

Overview

NCRP Report No. 180 contains NCRP's recommendations to guide active decision-making for radiation protection. Key points for radiation protection in the NCRP guidance include:

- the best protection guidelines are flexible and reflect current circumstances;
- new topics are addressed that have emerged in the last 25 years; and,
- medical use, stakeholder engagement, ethical values and safety culture are included and emphasized.

NCRP recommendations are intended to provide a basis for radiation protection programs in the United States. Report No. 180 is primarily for federal and state agencies responsible for the well being of individuals exposed to ionizing radiation and those agencies with responsibility for protecting non-human biota from such sources. The report also provides useful information for health physicists, medical physicists, physicians and other medical professionals, radiation safety officers, managers, workers, members of the public and the media.

Some of the categories of radiation protection that are discussed in NCRP Report No. 180 include: medicine; worker safety and naturally occurring radioactive materials; public safety, including sensitive populations; environmental protection; emergency response; and, research and industry.

Issues and Analysis

NCRP Report No. 180 gives an integrated and coherent approach for radiation protection in all exposure situations. The report states that optimization of protection universally applies, ensuring benefits from radiation taking into consideration societal, economic, and environmental aspects; addressing all hazards; and, striving for continuous improvement when it is reasonable to do so.

The report includes numeric criteria for individual dose management that provide an adequate basis for protection. The recommended criteria are influenced by the type and knowledge of the source; the existence of an appropriate radiation control program; and, whether that program can be established in advance of introducing the source.

NCRP Report No. 180 also includes new topics that have emerged in the last 25 years and builds on the many NCRP recommendations issued since the previous recommendations in Report No. 116, which was issued in 1993. The treatment of medical exposure is significantly expanded, including optimization for patients; coverage of comforters and caregivers; and, biomedical research participants. Emergency workers are defined as a new category of exposure and NCRP recommends that they be handled separately from occupational exposure or public protection. Protection of the environment, including non-human biota, is covered with recommendations to support decision-making under the National Environmental Policy Act (NEPA).

Ethical values, stakeholder engagement and safety culture are emphasized as contributing to radiation protection decisions and practice in addition to the knowledge of human biological effects of ionizing radiation. Ethical values support decision-making in complex situations. Stakeholders are key in making decisions concerning the management of their radiation exposure and the achievement of sustainable and suitable decisions. A strong safety culture is intrinsic to effective radiation protection programs.

Background

NCRP is a Congressionally chartered body that seeks to formulate and widely disseminate information, guidance and recommendations on radiation protection and measurements which represent the consensus of leading scientific thinking.

For additional information about NCRP, interested stakeholders may contact Laura Atwell, Director of Operations, at (301) 657-2652 (ext. 18) or at atwell@ncrponline.orgor go to http://ncrponline.org.

February 5, 2019

Todd D. Lovinger, Esq.
Executive Director
LLW Forum, Inc.
(754) 779-7551

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 10/3/2018 3:52:30 PM
To: Edwards, Jonathan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3715bc4dfc3e4d6caf3af1bf2fc5ca77-JEdwar02]
CC: Veal, Lee [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eb5e1fde4d7041539934f58976a20fc2-Veal, Lee]; Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Millett, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c067caa6c93544f78c26ab08cc567d27-Millett, John]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
Subject: Re: Correction: EPA-Radiation Rollback story

You' re right. I think OPA may be issuing a release to highlight the correction and further clarify (including statements provided to reporter that made that issue very clear).

> On Oct 3, 2018, at 11:50 AM, Edwards, Jonathan <Edwards.Jonathan@epa.gov> wrote:
>
> Additionally, the reporter mistakenly frames the April science proposal as a "radiation regulation." I know John K. was trying to get the reporter to correct her framing of the issue. -- Jon
>
> -----Original Message-----
> From: Veal, Lee
> Sent: Wednesday, October 03, 2018 11:20 AM
> To: Woods, Clint <woods.clint@epa.gov>; Wehrum, Bill <Wehrum.Bill@epa.gov>; Millett, John <Millett.John@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
> Subject: Correction: EPA-Radiation Rollback story
>
> Clint,
> Thank you (and John Konkus). We are receiving a number of calls from federal partners about this article, and this correction will help. As you know, NRC, DOE and other federal partners all use the LNT model.
>
> Lee
>
> Lee Ann B. Veal
> Director, Radiation Protection Division
> Office of Radiation and Indoor Air
> Office: 202-343-9448; Cell: 202-617-4322 www.epa.gov/radiation
>
> -----Original Message-----
> From: Woods, Clint
> Sent: Wednesday, October 03, 2018 10:39 AM
> To: Wehrum, Bill <Wehrum.Bill@epa.gov>; Millett, John <Millett.John@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
> Subject: Correction: EPA-Radiation Rollback story
>
> FYI
> https://apnews.com/6a573b6b020e453c90ecd5e84aa23f57

Message

From: Harlow, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B5A9A34E31FC4FE6B2BEADDDA2AFFA44-HARLOW, DAV]
Sent: 12/13/2018 5:53:43 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]
Subject: EPA document
Attachments: childrens_supplement_final.pdf; ATT00001.htm

Bill,

Here is the document that from 2005 that Ms. McConaghy mentioned.

Sent from my iPhone

Begin forwarded message:

> **From:** "Harlow, David" <harlow.david@epa.gov>
> **Date:** December 13, 2018 at 12:47:52 PM EST
> **To:** "Harlow, David" <harlow.david@epa.gov>
> **Subject: Document**
>
> https://www.epa.gov/sites/production/files/2013-09/documents/childrens_supplement_final.pdf

EPA/630/R-03/003F
March 2005

Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

AUTHORS AND CONTRIBUTORS

This document was prepared by a Technical Panel of the Risk Assessment Forum.

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CONTRIBUTORS

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ACKNOWLEDGMENTS

We would especially like to thank David Bennett for his earlier work in leading the initial efforts for this work, Bill Wood for his support, and Julian Preston for his helpful review of the document. Special thanks also go to Rebecca Brown, Rosemary Castorina, Ellen Phelps, and Linda Poore for their efforts in pulling together the underlying information.

CONTENTS

PREFACE vi

1. INTRODUCTION 1
2. PROCEDURES 6
   2.1. DATA SOURCES FOR ANIMAL STUDIES 6
   2.2. EVALUATING THE MODE OF ACTION OF CARCINOGENS 8
   2.3. QUANTITATIVE METHODS 9
   2.4. IONIZING RADIATION 12
3. RESULTS 13
   3.1. QUALITATIVE EVALUATION OF THE DATABASE 13
   3.2. QUANTITATIVE EVALUATION OF THE DATABASE 15
      3.2.1. Carcinogens with a Mutagenic Mode of Action 16
         3.2.1.1. *Early Postnatal, Juvenile, and Adult Repeated Dosing Studies of Chemicals with a Mutagenic Mode of Action* 16
         3.2.1.2. *Acute Dosing Studies of Chemicals with a Mutagenic Mode of Action* 17
      3.2.2. Carcinogens with Modes of Action Other Than Mutagenicity 19
      3.2.3. Ionizing Radiation 21
4. DISCUSSION 23
5. GUIDANCE FOR ASSESSING CANCER RISKS FROM EARLY-LIFE EXPOSURE 30
6. COMBINING LIFESTAGE DIFFERENCES IN EXPOSURE AND DOSE-RESPONSE WHEN ASSESSING CARCINOGEN RISK - SOME EXAMPLES FOR CARCINOGENS THAT ACT THROUGH A MUTAGENIC MODE OF ACTION 36
   6.1 CALCULATING LIFETIME RISKS ASSOCIATED WITH LIFETIME EXPOSURES 36
   6.2 CALCULATING LIFETIME RISKS ASSOCIATED WITH LESS THAN LIFETIME EXPOSURES 368

APPENDIX A: TABLES A-1

Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles...A-1

Table 1b. List of chemicals considered in this analysis. (These are chemicals for which there are both early-life and adult exposure reported in the same animal experiment.)......... ....A-3

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures..A-5

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure...A-17

Table 4. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to carcinogens with a mutagenic mode of action....................A-44

Table 5: Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to chemicals with other than mutagenic modes of action.......A-45

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to chemicals with mutagenic modes of action.....................A-46

Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult...A-57

Table 8. Summary of quantitative estimates of ratio of early-life to adult cancer potencies...A-60

Table 9. Excess Relative Risk (ERR) estimates for cancer incidence from Life Span Study (Japanese survivors)..A-61

Table 10. Excess Relative Risk estimates for incidence of thyroid cancer from Life Span Study...A-62

Table 11. Coefficients for the Revised Methodology mortality risk model (from U.S. EPA, 1999)...A-63

REFERENCES R-1

LIST OF FIGURES

Figure 1. Flow chart for early-life risk assessment using mode of action framework 42

Figure 2. Posterior, unweighted geometric means and 95% confidence intervals for the ratios of juvenile to adult cancer potency for carcinogens acting primarily through a mutagenic mode of action... 43

Figure 3. Study designs 44

PREFACE

U.S. Environmental Protection Agency (EPA or the Agency) cancer risk assessments may be conducted differently than envisioned in this Supplemental Guidance for many reasons including, for example, new information, new scientific understanding, or different science policy judgment. The practice of risk assessment with respect to accounting for early-life exposures to toxicants continues to develop, and specific components of this Supplemental Guidance may become outdated or may otherwise require modification in individual settings. It is EPA's intent to use, to the extent practicable and consistent with Agency statutes and regulations, the best available science in its risk assessments and regulatory actions, and this Supplemental Guidance is not intended to provide any substantive or procedural obstacle in achieving that goal. Therefore, the Supplemental Guidance has no binding effect on EPA or on any regulated entity. Where EPA does use the approaches in the Supplemental Guidance in developing risk assessments, it will be because EPA has decided in the context of that risk assessment that the approaches from the Supplemental Guidance are suitable and appropriate. This judgment will be tested through peer review, and the risk assessment will be modified to use different approaches if appropriate.

This Supplemental Guidance is intended for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and has no binding effect on EPA or any regulated entity, but instead represents a non-binding statement of policy.

The Supplemental Guidance addresses a number of issues pertaining to cancer risks associated with early-life exposures generally, but provides specific guidance on potency adjustment only for carcinogens acting through a mutagenic mode of action. This guidance recommends for such chemicals, a default approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure. Default adjustment factors are meant to be used only when no chemical-specific data are available to assess directly cancer susceptibility from early-life exposure to a carcinogen acting through a mutagenic mode of action.

The Agency considered both the advantages and disadvantages of extending the recommended, age dependent adjustment factors for carcinogenic potency to carcinogenic agents for which the mode of action remains unknown. EPA recommends these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and long-standing science policy positions that set out the Agency's overall approach to carcinogen risk assessment, e.g., the use of a linear, no threshold extrapolation procedure in the absence of data in order to be health protective. In general, the Agency prefers to rely on analyses of data rather than on general defaults. When data are available for a susceptible lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation per the Agency's *Guidelines for Carcinogen Risk Assessment*, a linear low-dose extrapolation methodology is recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life susceptibility or when the mode of action is not mutagenicity.

The Agency expects to produce additional supplemental guidance for other modes of action, as data from new research and toxicity testing indicate it is warranted. EPA intends to focus its research, and to work collaboratively with its federal partners, to improve understanding of the implications of early life exposure to carcinogens. Development of guidance for estrogenic agents and chemicals acting through other processes resulting in endocrine disruption and subsequent carcinogenesis, for example, might be a reasonable priority in light of the human experience with diethylstilbesterol and the existing early-life animal studies. It is worth noting that each mode of action for endocrine disruption will probably require separate analysis.

As the Agency examines additional carcinogenic agents, the age groupings may differ from those recommended for assessing cancer risks from early-life exposure to chemicals with a mutagenic mode of action. Puberty and its associated biological changes, for example, involve many biological processes that could lead to changes in susceptibility to the effects of some carcinogens, depending on their mode of action. The Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework described in the Agency's *Guidelines for Carcinogen Risk Assessment* is an appropriate mechanism for elucidating these lifestages. For each additional mode of action evaluated, the various age groupings determined to be at differential risk may differ from those described in this Supplemental Guidance. For example, the age groupings selected for the age-dependent adjustments were initially selected based on the available data, i.e., for the laboratory animal age range representative of birth to < 2 years in humans. More limited data and information on human biology are being used to determine a science-informed policy regarding 2 to < 16 years. Data were not available to refine the latter age group. If more data become available regarding carcinogens with a mutagenic mode of action, consideration may be given to further refinement of these age groups.

Access to data and other information relating to the Cancer Guidelines (U.S. EPA, 2005) and this Supplemental Guidance will be through EPA's Risk Assessment Forum website, under Publications, Guidelines, Guidelines for Cancer Risk Assessment. The URL is http://www.epa.gov/cancerguidelines. The data and results of analyses are available in spreadsheets.

1. INTRODUCTION

Cancer risk to children in the context of the U.S. Environmental Protection Agency's cancer guidelines (U.S. EPA, 2005) includes both early-life exposures that may result in the occurrence of cancer during childhood and early-life exposures that may contribute to cancers later in life. The National Research Council (NRC, 1994) recommended that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." This document focuses on cancer risks from early-life exposure compared with those from exposures occurring later in life. Evaluating childhood cancer and childhood exposures resulting in cancer later in life are related, but separable, issues.

Historically, the focus on cancer has been as a disease associated with aging, resulting from extended exposure duration with prolonged latency periods before the cancers appear. Because much of cancer epidemiology addresses occupational exposures and because rodent cancer studies are designed to last approximately a lifetime (two years) beginning after sexual maturity, the cancer database used by EPA and other agencies for risk assessment focuses on adults. However, extensive literature demonstrates that exposures early in life (i.e., transplacental or *in utero*, early postnatal, lactational) in animals can result in the development of cancer (reviewed in Toth, 1968; Della Porta and Terracini, 1969; Druckery, 1973; Rice, 1979; Vesselinovitch et al., 1979; Rice and Ward, 1982; Vesselovitch et al., 1983; Anderson et al., 2000). Thus, one element in extending analyses to children is to evaluate the extent to which exposures early in life would alter the incidence of cancers observed later in life, compared with the incidence observed with adult-only exposures (Anderson et al., 2000; NRC, 1993).

The causes of cancer encompass a variety of possible risk factors, including genetic predisposition (Tomlinson et al., 1997), diet, lifestyle, associations with congenital malformations (Bosland, 1996), and exposure to biological and physical agents and chemicals in the environment. In some cases, tumors in adults and children have been compared (Anderson et al., 2000; Ginsberg et al., 2002). Children and adults generally develop the same spectrum of tumors when they have inherited gene and chromosomal mutations, such as Li-Fraumeni syndrome (Birch et al., 1998). With ionizing radiation, which operates through a mutagenic mode of action, both the young and the old develop many of the same tumors, with the difference being that children are more susceptible for a number of tumor types (NRC, 1990; U.S. EPA, 1994; UNSCEAR, 2000). Studies with anticancer drugs (cytotoxic and immunosuppressive) demonstrate a similar spectrum of tumors (Hale et al., 1999; Kushner et al., 1998; Larson et al., 1996; Nyandoto et al., 1998). Various viral infections, such as Epstein Barr and hepatitis B, lead to lymphoma and liver cancer, respectively, in both age groups (Lindahl et al., 1974; Mahoney, 1999). These observations in humans indicate that the mode of action for these agents would be the same or similar for adults and children.

Although there are similarities between childhood and adult tumors, significant differences are also known to exist (Grufferman, 1998; Israel, 1995). Tumors of childhood generally consist more of embryonic cell tumors, while adults have more carcinomas. Leukemias, brain and other nervous system tumors, lymphomas (lymph node cancers), bone cancers, soft tissue sarcomas, kidney cancers, eye cancers, and adrenal gland cancers are the most common cancers of children, while skin, prostate, breast, lung, and colorectal cancers are the most common in adults (Ries et al., 1999; U. S. Cancer Statistics Working Group, 2002). Some tumors are unique to the young, including several with well established genetic bases, such as tumors of the kidney (Wilms' tumor) or eye (retinoblastoma) (Anderson et al., 2000; Israel, 1995).

The relative rarity in the incidence of childhood cancers and a lack of animal testing guidelines with perinatal[1] exposure impede a full assessment of children's cancer risks from exposure to chemicals in the environment. Unequivocal evidence of childhood cancer in humans occurring from chemical exposures is limited (Anderson et al., 2000). Established risk factors for the development of childhood cancer include radiation and certain pharmaceutical agents used in chemotherapy (Reise, 1999). There is some evidence in humans for adult tumors resulting from perinatal exposure. Pharmacological use of diethylstilbesterol (DES) during pregnancy to prevent miscarriages induced clear cell adenocarcinoma of the vagina in a few daughters exposed *in utero* though this tumor was not observed in exposed mothers (Hatch et al., 1998; Robboy et al., 1984; Vessey, 1989). In addition to the limited human data, there are examples of transplacental carcinogens in animal studies, such as recent studies with nickel and arsenic (Diwan et al., 1992; Waalkes et al., 2003), as well as studies suggesting that altered development can affect later susceptibility[2] to cancer induced by exposure to other chemicals (Anderson et al., 2000; Birnbaum and Fenton, 2003).

Infrequently, perinatal exposure in animals has been shown to induce tumors of different types than those observed with adult exposures. Studies with saccharin (Cohen et al., 1995; Whysner and Williams, 1996; IARC, 1999) and ascorbate (Cohen et al., 1998; Cohen et al., 1995; NTP, 1983) found cancer when exposures were initiated in the perinatal period. In

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[1] Perinatal is defined as the time around birth and may include both prenatal (prior to birth) and postnatal (after birth) periods.

[2] Susceptibility is defined here as an increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human subpopulation (e.g., lifestage, demographic feature, or genetic characteristic). The terms "susceptibility" and "sensitivity" are used with a variety of definitions in published literature making it essential that readers are aware of these differences in terminology across documents.

contrast, studies submitted to the Food and Drug Administration of approximately a dozen other food additives and colorings that were not adult carcinogens did not indicate cancer, even when perinatal exposures occurred (U.S. EPA, 1996). When observed, the differences between childhood and adult cancers suggest the importance of evaluating the impacts of maternal exposures during pregnancy as well as exposures to children (Anderson et al., 2000). The effects of maternal exposures and transplacental carcinogens require separate evaluation and are not quantitatively evaluated in the analysis presented below.

The limited human information described briefly above is supported by a number of animal bioassays that include both perinatal and adult exposures to chemicals. Standard animal bioassays generally begin dosing after the animals are 6-8 weeks old, when many organs and systems are almost fully developed, though substantial growth in body size continues thereafter (as more fully discussed in Hattis et al., 2005). The literature can be divided roughly into three types of exposure scenarios: those that include *repeated* exposures for the early postnatal to juvenile period, as compared with chronic later-life dosing; *lifetime* (i.e., combined perinatal and adult) exposure as compared with chronic later-life dosing; and those that include more *acute* exposures, such as a single intraperitoneal (ip) or subcutaneous injection, for both early-life and later-life dosing. In the early-life exposure studies that are available, perinatal exposure usually induces higher incidence of tumors later in life than the incidence seen in standard bioassays where adult animals only were exposed; some examples include diethylnitrosamine (DEN) (Peto et al., 1984), benzidine (Vesselinovitch et al., 1979), DDT (Vesselinovitch et al., 1979), and polybrominated biphenyls (PCBs) (Chhabra et al., 1993a). Reviews comparing early-life carcinogenesis bioassays with standard bioassays for a limited number of chemicals (McConnell, 1992; Miller et al., 2002; U.S. EPA, 1996) have concluded:

- The same tumor sites usually are observed following either perinatal or adult exposure.
- Perinatal exposure in conjunction with adult exposure usually increases the incidence of tumor bearing animals or reduces the latent period before tumors are observed.

There is limited evidence to inform the mode(s) of action leading to differences in tumor type and tumor incidence following early-life exposure and exposure later in life. Differences in the capacity to metabolize and clear chemicals at different ages can result in larger or smaller internal doses of the active agent(s), either increasing or decreasing risk (Ginsberg et al., 2002; Renwick, 1998). There is reason to surmise that some chemicals with a mutagenic mode of action, which would be expected to cause irreversible changes to DNA, would exhibit a greater effect in early-life versus later-life exposure. Several studies have shown increased susceptibility of weanling animals to the formation of DNA adducts following exposure to vinyl chloride (Laib et al., 1989; Morinello et al., 2002a; Morinello et al., 2002b). Additionally, even though not used quantitatively in the analyses in this document, a recent analysis of *in vivo* transplacental micronucleus assays indicated that fetal tissues generally are more sensitive than maternal tissues for induction of micronuclei from mutagenic chemicals (Hayashi et al., 2000), providing qualitative support for the early-life susceptibility. Similarly, the neonatal mouse model for carcinogenesis, which uses two doses prior to weaning followed by observation of tumors at one year, shows carcinogenic responses for mutagenic agents (Flammang et al., 1997; McClain et al., 2001). These results are consistent with the current understanding of biological processes involved in carcinogenesis, which leads to a reasonable expectation that children can be more susceptible to carcinogenic agents than adults (Anderson et al., 2000; Birnbaum and Fenton, 2003; Ginsberg, 2003; Miller et al., 2002; Scheuplein et al., 2002). Some aspects potentially leading to childhood susceptibility include the following issues.

- More frequent cell division during development can result in enhanced fixation of mutations due to the reduced time available for repair of DNA lesions and clonal expansion of mutant cells gives a larger population of mutants (Slikker et al, 2004).
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al., 2003).
- Hormonal systems operate at different levels during different lifestages (Anderson et al., 2000).
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).

The methodology that has been generally used by the U.S. EPA to estimate cancer risk associated with oral exposures relies on estimation of the lifetime average daily dose, which can account for differences between adults and children with respect to exposure factors such as eating habits and body weight. However, susceptibility differences with respect to early lifestages are not taken into consideration because cancer slope factors[3] are based upon effects

[3] Cancer slope factor – An upper bound estimate of the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per unit exposure (e.g., mg/kg-day or ug/m^3), is generally reserved for use in the low-dose region of the dose-response relationship. It is often the statistical upper bound on the potency and therefore the risk. "Upper bound" in this context is a plausible

observed following exposures to adult humans or sexually mature animals. Since a much larger database exists for chemicals inducing cancer in adult humans or sexually mature animals, it is necessary to determine whether adjustment of such adult-based cancer slope factors would be appropriate when assessing cancer risks associated with exposures early in life. The analysis undertaken here addresses this issue, focusing upon studies that define the potential duration and degree of increased susceptibility that may arise from childhood, defined as early-life (typically postnatal and juvenile animal) exposures. Some of these analyses, along with a more complete description of the procedures used, have been published (Barton et al., 2005). The analysis presented in this Supplemental Guidance and in the published article form the basis for developing Supplemental Guidance for evaluating cancer susceptibility associated with early-life exposures.

upper limit to the true probability.

2. PROCEDURES

This section describes the steps taken to assess potential susceptibility to early-life exposure to carcinogenic compounds compared with adult and whole-life exposure. The readily available literature was reviewed to identify animal studies that compared tumor incidence between early-life and adult-only exposures or between early-life-and-adult and adult-only exposures. Studies were categorized by length of exposure; those studies with quantitative information to estimate tumor incidence over time for early-life and adult exposures were identified. These studies provided the basis for quantitatively estimating the difference in susceptibility between early-life and adult exposures, as described below. Finally, summaries of available human data for radiation exposure were reviewed in the context of tumor incidence from early-life versus later-in-life exposure.

2.1. DATA SOURCES FOR ANIMAL STUDIES

Studies in the literature included in this analysis are those that report tumor response from experiments that included both early-life and adult exposure as separate experimental groups. Initial studies for consideration were identified through review articles and a search of the National Toxicology Program (NTP) database. Reviews of the literature regarding cancer susceptibility from early-life exposure in animals include McConnell (1992), Ginsberg (2003), Anderson et al. (2000), Miller et al. (2002) and U.S. EPA (1996). A literature search was conducted utilizing key words and MeSH headings (Medline) from studies identified in the available reviews. The list of chemicals included in this analysis for quantitative evaluation is shown in Table 1a and 1b.

Abstracts or papers were reviewed to determine if a study provided information that could be used for quantitative analysis. The criteria used to decide if a study could be included in the quantitative analysis were:

- Exposure groups at different post-natal ages in the same study or same laboratory, if not concurrent (to control for a large number of potential cross-laboratory experimental variables including pathological examinations),
- Same strain/species (to eliminate strain-specific responses confounding age-dependent responses),
- Approximately the same dose within the limits of diets and drinking water intakes that obviously can vary with age (to eliminate dose-dependent responses confounding age-dependent responses),

- Similar latency period following exposures of different ages (to control for confounding latency period for tumor expression with age-dependent responses), arising from sacrifice at >1 year for all groups exposed at different ages, where early-life exposure can occur up to about 7 weeks. Variations of around 10 to 20% in latency period are acceptable,

- Postnatal exposure for juvenile rats and mice at ages younger than the standard 6 to 8 week start for bioassays; prenatal (*in utero*) exposures are not part of the current analysis. Studies that have postnatal exposure were included (without adjustment) even if they also involved prenatal exposure,

- "Adult" rats and mice exposure beginning at approximately 6 to 8 weeks old or older, i.e. comparable to the age at initiation of a standard cancer bioassay (McConnell, 1992). Studies with animals only at young ages do not provide appropriate comparisons to evaluate age-dependency of response (e.g., the many neonatal mouse cancer studies). Studies in other species were used a supporting evidence, because they are relatively rare and the determination of the appropriate comparison ages across species is not simple, and

- Number of affected animals and total number of animals examined are available or reasonably reconstructed for control, young, and adult groups (i.e., studies reporting only percent response or not including a control group would be excluded unless a reasonable estimate of historical background for the strain was obtainable).

Tables 2 and 3 include information on the methods and results from the animal studies identified in Table 1b. Pertinent information on species, sex, dosing regimen, and tumor incidence is given. Additionally, the "Notes" column includes general information about the relationship between tumor incidence, animal age at first dosing, and sex. The data in Tables 2 and 3 were used for the calculations, described below, for estimating potentially increased cancer risk from early-life exposure.

The available literature includes a wide range of exposure scenarios. This range is due in part to the lack of a defined protocol for early-life testing and the difficulty of standardizing and administering doses preweaning. As noted previously, the literature can be divided roughly into three types of exposure scenarios: those that include repeated exposures for the early postnatal to juvenile period, as compared with chronic later-life dosing; lifetime (i.e., combined perinatal and adult) exposure as compared with chronic later-life dosing; and those that include more acute exposures, such as a single intraperitoneal (ip) or subcutaneous injection, for both early-life and later-life dosing. Table 2 includes the studies that had early postnatal to juvenile exposures, adult chronic exposures, and lifetime exposures. Table 3 includes studies with acute exposures. A discussion of the implications of the different exposure scenarios is included in Section 3.

Studies were identified for more than 50 chemicals not included in Tables 2 and 3 that demonstrated carcinogenesis following perinatal exposure, but did not directly compare exposures at different ages. A large number of studies address *in utero* exposures only. More than 100 chemicals (with both negative and positive findings) have been studied in the neonatal mouse assay, but this assay does not have a comparable adult exposure (Flammang et al., 1997; McClain et al., 2001; Fujii, 1991). Studies across laboratories often varied in their use of animal strains (e.g., for AZT studies, Diwan et al., 1999 used CD-1 mice, while NTP, 1999 used $B6C3F_1$ mice). Studies of tamoxifen use two Wistar-derived strains and had very different periods for tumor expression, i.e., sacrifice at 20 months for adult-exposed rats and natural death up to 35 months for juvenile-exposed rats, with uterine tumors observed in animals dying after 22 months (Carthew et al., 2000; Carthew et al., 1996; Carthew et al., 1995). Due to these factors, the chemicals that belong to this group were not evaluated quantitatively. In addition, there were studies assessing radiation in animals (Covelli et al., 1984; Di et al., 1990; Sasaki et al., 1978). The radiation data were not analyzed in depth, in part because there are recognized differences in toxicokinetics and toxicodynamics between radiation and chemicals with a mutagenic mode of action for carcinogenesis. Even though the data on A-bomb survivors provide information for many different cancer sites in humans with a single exposure involving all ages, a number of national and international committees of experts have analyzed and modeled these data to develop risk estimates for various specific applications. Furthermore, lack of uniformity regarding radiation doses, gestational age at exposure, and the animal strains used make it difficult to make comparisons across studies (Preston et al., 2000).

2.2. EVALUATING THE MODE OF ACTION OF CARCINOGENS

Evaluation of the mode of action of a carcinogen was based upon a weight-of-evidence approach. Multiple modes of action are associated with the chemicals in this database, but a number are associated with mutagenicity (i.e., benzo(a)pyrene, benzidine, dibenzanthracene, diethylnitrosamine, dimethylbenz(a)anthracene, dimethylnitrosamine, ethylnitrosourea, 3-methylcholanthrene, methylnitrosourea, safrole, urethane, and vinyl chloride). Determination of carcinogens that are operating by a mutagenic mode of action entails evaluation of short-term testing results for genetic endpoints, metabolic profiles, physicochemical properties, and structure-activity relationship (SAR) analyses in a weight-of-evidence approach (Dearfield et al., 1991; U.S. EPA, 1986, 1991; Waters et al., 1999), as has been done for several chemicals (e.g., Dearfield et al., 1999; McCarroll et al., 2002; U.S. EPA, 2000a). Key data for a mutagenic mode of action may be evidence that the carcinogen or a metabolite is DNA reactive and/or has the ability to bind to DNA. Also, such carcinogens usually produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo* which generally are supported by positive tests *in vitro*. Additionally, carcinogens may be identified as operating via a mutagenic mode of action if they have similar properties and SAR to established mutagenic mode of action.

2.3. QUANTITATIVE METHODS

To estimate the potential difference in susceptibility between early-life and adult exposure, we calculated the estimated ratio of the cancer potency from early-life exposure compared to the estimated cancer potency from adult exposure. The cancer potency was estimated from a one-hit model, or a restricted form of the Weibull model, which is commonly used to estimate cumulative incidence for tumor onset. The general form of the equation is:

P(dose) = 1-[1-P(0)]exp(-cancer potency*dose)

The ratio of juvenile to adult cancer potencies were calculated by fitting this model to the data for each age group. The model fit depended upon the design of the experiment that generated the data. Two designs should be handled separately: experiments in which animals are exposed either as juveniles or as adults (with either a single or multiple dose in each period), and experiments in which exposure begins either in the juvenile or in the adult period, but once begun, continues through life.

For the first case, the model equations are:

$$\begin{aligned} P_A &= P_0 + (1-P_0)(1-e^{-m_A \delta_A}) \\ P_J &= P_0 + (1-P_0)\left(1-e^{-m_A e^{\lambda} \delta_J}\right) \end{aligned} \qquad (1)$$

where:

subscripts A and J refer to the adult and juvenile period, respectively,
λ is the natural logarithm of the juvenile:adult cancer potency ratio,
P_0 is the fraction of control animals with the particular tumor type being modeled,
P_x is the fraction of animals exposed in age period x with the tumor,
m_A is the rate of accumulation of "hits" per unit of time for adults, i.e., the cancer potency, and
δ_x is the duration or number of exposures during age period x.

For a substantial number of data sets (acute exposures), $\delta_J = \delta_A = 1$. We are interested in determining λ, which is the logarithm of the estimated ratio of juvenile to adult cancer potencies, a measure of potential susceptibility for early-life exposure.

For the second kind of design, the model equations should take into account that exposures that were initiated in the juvenile period continue through the adult period. The model equations for the fraction of animals exposed only as adults with tumors in this design are the same as in the first design, but the fraction of animals whose first exposure occurred in the juvenile period is:

$$P_J = P_0 + \left(1 + P_0\right)\left(1 - e^{-m_A e^{\lambda}(\delta_J - \delta_A) - m_A \delta_A}\right) \tag{2}$$

All symbols in (eq. 2) have the same interpretation as their counterparts in (eq. 1), but now δ_J includes the duration of exposure during the juvenile period as well as the subsequent adult period.

Parameters in these models were estimated using Bayesian methods (see, for example, Carlin and Louis, 2000), and all inferences about the ratios were based on the marginal posterior distribution of λ. Some of these analyses, including a more complete description of the procedures (including the potential effect of alternative Bayesian priors that have been examined) have been published (Barton et al., 2005). The data for estimating each ratio were in the form of numbers of animals tested and number affected for each of control, juvenile-exposed, and adult-exposed animals, and duration of exposure for each of the juvenile-exposed and adult-exposed groups. A few data sets had separate control groups for the juvenile-exposed and adult-exposed groups, and equations 1 and 2 were modified accordingly. The likelihood for the parameters in the model was the product of three (or four, if there were two control groups) binomial probabilities: for the number of animals with tumors in the control group(s), for the juvenile-exposed group, and for the adult-exposed group. The prior for P_0 (the fraction of control animals with a particular tumor) was right triangular (right angle at the origin), based on the assumption that control incidences should be relatively low. (The base of the distribution is one, as P_0 can not exceed one. As this is a probability distribution, the area of the triangle is one. Therefore, its height at the origin must be 2.) The effect of exposure in adults is quantified by the extra risk, Q, where the probability that an animal has a tumor is $P_0+(1-P_0)Q$. So, from equations 1, $Q = 1 - e^{-m_A \delta_A}$, Q was given a uniform prior on the interval (0,1), reflecting total ignorance about the extra risk of adult exposure. Finally, the prior for λ was Gaussian with mean 0 (corresponding to a median or geometric mean ratio of one) and standard deviation 3. The prior for the log ratio of juvenile to adult cancer potency has some influence over the posterior estimates for the ratio of juvenile to adult potency. The magnitude of that influence depends on the amount of support in the data for different values of the log ratio. The prior also effectively downweights extremely large or small values for the juvenile to adult potency ratio. Three priors for the standard deviation were evaluated (Barton et al., 2005, see Appendix), with the intent of finding the largest prior, i.e., one that would contain the least informative assumption for the prior. A standard deviation of 9 was tried, but some of the intervals would not converge. A standard deviation of 3 worked well, allowed ratio estimates to be derived, with all of the data of interest. An intermediate value of 6 was also examined to ascertain if a less informative prior could be used. While the intervals converged, a sensitivity analysis showed that this value for the standard deviation resulted in sufficient down-weighting of the ratios with limited information that these data would not influence the result. This was considered an unreasonable bias, so a standard deviation of 3 was used for the further analyses. A further discussion of these analyses can be found in Barton et al. (2005).

The posterior distribution for the unknown parameters in these models is the product of the likelihood from the data and the priors (the "unnormalized" prior), divided by a normalization constant that is the integral of the unnormalized prior over the ranges of all the parameters. This normalization constant was computed using numerical integration, as were posterior means and variances and marginal posterior quantiles for the log-ratio λ. All numerical computations were carried out in the R statistical programming language (version 1.8.1; R Development Core Team, 2003).

This method produced a posterior mean ratio of the early-life to adult cancer potency, which is an estimate of the potential susceptibility of early-life exposure to carcinogens. If the ratio was greater than one, this indicated that the experiment found that there was greater susceptibility from early-life exposure. If the ratio was less than one, this indicated that the experiment found that there was less susceptibility from early-life exposure. Summaries of the individual ratios from each of the dose groups from the different experiments for different groupings were also calculated (for example for all acute exposures of chemicals that are carcinogenic by a mutagenic mode of action). The summary ratios were constructed from the individual ratios within a group, by variance-weighting the means of each ratio. The individual, posterior means were weighted by using reciprocals of their posterior variance. This weighting procedure is commonly used because it gives greater weight to those studies for which the variances, i.e., the uncertainties, are smaller. Because the ratios were calculated as log ratios (see eq. 1), exponentiating the resulting inverse-variance-weighted mean yielded inverse-variance-weighted geometric means of ratios.

2.4. IONIZING RADIATION

A supporting role was assigned to the available human radiation data, where cancer incidence in adults who were children at the time of the atomic bomb (A-bomb) exposure was compared with cancer incidence in adults who were older at the time of exposure. Although there are recognized differences in toxicokinetics and toxicodynamics between radiation and chemical carcinogens with a mutagenic mode of action, the data on A-bomb survivors provide information for many different cancer sites in humans with a single exposure involving all ages. In addition to the richness of the data, a number of national and international committees of experts have analyzed and modeled these data to develop risk estimates for various specific applications.

The report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000, with Scientific Annexes) lists more than 80 studies, in addition to the reports of the Japanese A-bomb survivors, in which at least one type of cancer was measured in humans who were exposed either intentionally or accidentally to some form of ionizing radiation. However only the A-bomb survivor reports have relevant information on incidence of early-life exposures. One of the more recent papers cited in the UNSCEAR report, by Thompson et al. (1994), contains detailed data on the incidence of 21 different cancers in 37,270 exposed A-bomb survivors (42,702 unexposed). Also, EPA has used data from the A-bomb survivors to develop age-specific relative risk coefficients using various methods for transporting the risk from the Japanese population to the U.S. population (U.S. EPA, 1994). It is beyond the scope of this effort to present all of the radiation data or a discussion of the various analyses and modeling efforts. Rather, information relevant to comparing cancer risks from juvenile versus adult exposure from UNSCEAR (2000) and U.S. EPA (1994; 1999) is presented as representative findings to determine whether the radiation data are similar qualitatively to the chemical findings. More detailed data on the A-bomb survivors can be found in Delongchamp et al. (1997) and Preston et al. (2000).

As previously noted, several studies have assessed radiation in animal studies (Covelli et al., 1984; Di et al., 1990; Sasaki et al., 1978). However, lack of uniformity regarding radiation doses, gestational age at exposure, and the animal strains used make it difficult to compare the experimental data on cancer induction after prenatal irradiation (Preston et al., 2000).

3. RESULTS

3.1. QUALITATIVE EVALUATION OF THE DATABASE

The question addressed in this analysis was whether, and how, available quantitative scientific data could inform risk assessment policy choices for adjusting cancer slope factors when they are used in the assessment of cancer risk from childhood exposure. Cancer slope factors are, with few exceptions, based on adult human epidemiology or standard chronic adult rodent bioassays, which do not address the impacts of early-life exposures. Thus, the critical data are either human epidemiological data on childhood exposures resulting in adult cancer or research studies with rodents involving early postnatal exposures. The major human data available are from radiation exposures (studies summarized in Tables 9-11), with very limited data available for humans exposed during childhood to chemicals (reviewed in Anderson et al., 2000; Miller et al., 2002).

A review of the literature identified several hundred references reporting more than 50 chemicals that have been shown to be able to cause cancer following perinatal exposure (Table 1a) (reviewed in Toth, 1968; Della Porta and Terracini, 1969; Druckery, 1973, Rice, 1979; Vesselinovitch et al., 1979; Rice and Ward, 1982; Vesselovitch et al.; 1983; Fujii, 1991; Anderson et al., 2000). Studies (or groups of studies from a single laboratory on a given chemical) that directly provided quantitative data on carcinogenesis following early postnatal exposures and adult exposures to chemicals in animals were identified for 18 chemicals, listed in Table 1b, 2, and 3. Of the identified studies, there were 11 chemicals involving repeated exposures during early postnatal and adult lifestages (Table 1b) and 8 chemicals using acute exposures (typically single doses) at different ages (Table 1b). Some of the studies evaluated single tissues or organs for tumors (e.g., only liver), while others evaluated multiple tissues and organs (Tables 2 and 3). Mice, rats, or both species and sometimes multiple strains were tested. These studies serve as the basis for the quantitative analyses presented later in the results.

In addition to the studies identified in Table 1b, studies were identified with early postnatal and early-life exposures that were evaluated qualitatively but not quantitatively. Some of these studies are notable and provide important supporting information. Two recent studies used transgenic mouse models for human tumors. Increased multiplicity of colon tumors was observed following earlier versus later azoxymethane exposures (Paulsen et al., 2003). Shortened mammary tumor latency following estradiol exposure occurred when exposures occurred between 8 and 18 weeks as opposed to earlier or later, which is generally consistent with the incidence results analyzed for DMBA (Yang et al., 2003). Several notable examples exist of developmental windows leading to cancer susceptibilities that were not observable in adults. Several potent estrogenic chemicals including DES, tamoxifen, and genistein produce uterine tumors with early postnatal exposures of mice, though there also appear to be strain-dependent differences in the tumor sites in adult mice (Gass et al., 1964; Greenman et al., 1990; Newbold et al., 1990, 1997, 1998, 2001). Developmental susceptibilities are believed to play a key role in effects observed with saccharin (Cohen et al., 1995; Whysner and Williams, 1996) and ascorbate (Cohen et al., 1998; NTP, 1983), with bladder tumors arising when early-life exposures occurred. Studies with several species, including rat, mouse, and opossum, indicate that nervous systems tumors associated with exposures to ENU and several other chemicals appear to be highly dependent upon exposures occurring within certain windows, particularly prenatal ones (Rice, 1979; Rice and Ward, 1982; Jurgelski et al., 1979).

Analyses of the difference in cancer risk from exposures during different lifetime periods ideally should address both the period of potential susceptibility and the magnitude of the susceptibility. Available studies used a variety of study designs (see Tables 2 and 3), which can be valuable because they provide different information (Figure 1). However, variations in study design can result in a lack of comparability across chemicals, and can limit information on the consistency of effects with different chemicals acting through different modes of action. The acute dosing (largely single dose) studies (Table 3) are valuable because they involve identical exposures with explicitly defined doses and time periods demonstrating that differential tumor incidences arise exclusively from age-dependent susceptibility. These studies address both the period and magnitude of susceptibility. They were not as appropriate for quantitative adjustments for the cancer potency estimates because of their limitations, including that most used subcutaneous or ip injection that historically have not been considered quantitatively relevant routes of environmental exposure for human cancer risk assessment by EPA, and that these routes of exposure are expected to have only partial or a complete absence of first pass metabolism that is likely to affect potency estimates.

The repeated dosing studies with exposures during early postnatal or adult lifetime provide useful information on the relative impact of repeated exposures at different lifestages and may be more likely to have exposure occur during a window of susceptibility, if there is one. One notable difference in study designs was that studies with repeated early postnatal exposure were included in the analysis even if they also involved earlier maternal and/or prenatal exposure, while studies addressing only prenatal exposure were not otherwise a part of this analysis. Another notable difference among studies involved the tissues that were evaluated for tumors: some studies focused on a single tissue, particularly liver, while others evaluated multiple tissues.

Comparisons within a single repeated dosing study may have limitations for evaluating differential susceptibility because exposures to the chemical can differ during the different lifestages, particularly when dietary or drinking water exposures are involved. A notable example is the PCB study (Chhabra et al., 1993a), in which mobilization of such lipid-soluble chemicals into mother's milk would be expected to result in infants receiving much larger exposures than other lifestages. While lactational transfer is just as relevant to human nursing offspring, this difference in exposure obscures the extent to which the early lifestage is quantitatively more susceptible (i.e., part of the increased early-life cancer risk arises from higher exposure than during the adult period). Maternal metabolism of compounds such as diphenylhydantoin (DPH) (Chhabra et al., 1993b) also may result in lower exposure during lactation, potentially underestimating the early-lifestage risk, if the parent compound is the active form of the chemical. Similar issues exist due to normal age-dependent changes in food and water consumption. Ascribing differential effects observed in animal studies solely to lifestage susceptibility must be done carefully as there may also be differences in the exposures. There are substantial and clear benefits, therefore, from experimental consistency when comparisons are made directly within a study (e.g., same species and strain, consistent pathological evaluation).

One issue to note is the rationale for the organization of the available data. It was observed that the results across a broad range of chemicals with a variety of modes of action were somewhat variable. Therefore, consistent with the approach of the EPA cancer guidelines (U.S. EPA, 2005), an approach based on mode of action appeared to be a common framework for analysis. Variability in lifestage-dependent susceptibility and susceptibility across a range of modes of action was further supported by theoretical analyses using multistage and two-stage models of carcinogenesis (Goddard and Krewski, 1995; Murdoch et al., 1992).

3.2. QUANTITATIVE EVALUATION OF THE DATABASE

As described in the Section 2.3, the potential difference in susceptibility between early-life and adult exposure was calculated as the estimated ratio of cancer potency from early-life exposure over the cancer potency from adult exposure. Tables 4-7 present the results of the quantitative analysis using the studies that were determined qualitatively to have appropriate study designs (Tables 2 and 3) containing sufficient information to analyze. Based on the studies available, the calculations were organized into four tables: (1) compounds acting through a primarily mutagenic mode of action, where the compound was administered by a chronic dosing regimen to adults and repeated dosing in the early postnatal period (Table 4); (2) compounds acting through a primarily nonmutagenic mode of action, where the compound was administered by a chronic dosing regimen to adults and repeated dosing in the early postnatal period (Table 5);

(3) compounds acting through a primarily mutagenic mode of action, where the compounds were administered by an acute dosing regimen (Table 6); and (4) compounds acting primarily through either a mutagenic or nonmutagenic mode of action with chronic adult dosing and repeated early postnatal dosing (Table 7). In these tables, the 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses. The results are discussed below, followed by a description of results from analyses of studies of humans exposed to radiation.

3.2.1. Carcinogens with a Mutagenic Mode of Action

The most informative database on early-lifestage susceptibility exists for chemicals with a well-accepted mutagenic mode of action (e.g., diethylnitrosamine, vinyl chloride). This database includes both single-dose studies and repeated-dose studies involving periods of postnatal and/or chronic exposure. These studies help define the periods of increased vulnerability and the magnitude of the susceptibility. The acute dosing studies demonstrate that the age-dependent responses are not due to differences in exposure, because these studies explicitly control the exposure.

3.2.1.1. *Early Postnatal, Juvenile, and Adult Repeated Dosing Studies of Chemicals with a Mutagenic Mode of Action*

Studies comparing repeated dosing for early-life, adult, or lifetime exposures exist for six carcinogens with a mutagenic mode of action [benzidine, diethylnitrosamine (DEN), 3-methylcholanthrene, safrole, urethane, and vinyl chloride]; DEN also had acute dosing studies. Lifetime (i.e., combined juvenile and adult) compared to adult exposure studies were analyzed for DEN, safrole, and urethane, while studies comparing juvenile with adult exposures were analyzed for benzidine, 3-methylcholanthrene, safrole, and vinyl chloride. These chemicals all require metabolic activation to the active carcinogenic form. Analysis of the tumors arising per unit time of exposure found that juvenile exposures with each chemical could be more effective than adult exposures were at inducing tumors (Tables 4 and 7; Figure 2, a graphic representation of the posterior, unweighted geometric means and their 95% confidence intervals, for the ratios of juvenile to adult cancer potency for carcinogens acting through a mutagenic mode of action). The weighted geometric mean for repeat and lifetime exposures is 10.4; for acute exposures the weighted geometric mean value is 1.5. For benzidine and safrole, there was a notable sex difference, with high liver tumor incidence observed for early postnatal exposures of male, but not female, mice. For both the acute and the repeated/lifetime data, the 95th percentile of the individual, unweighted geometric means is above 10 (Figure 2).

This analysis focused upon the duration of exposure as a surrogate for dose, essentially assuming that the doses animals received during the different periods of these studies were similar. This assumption is a limitation of the analysis because these studies involved exposures via lactation (i.e., dosing the mother prior to weaning), drinking water, diet, or inhalation, which have the potential to deliver different doses at different lifestages. However, the range of the magnitudes of the tumor incidence ratios of juvenile to adult exposures is similar (Table 8) for the repeated dosing studies (0.12 – 111, weighted geometric mean 10.5, 42% of ratios greater than 1), lifetime dosing studies (0.18 – 79, weighted geometric mean 8.7, 67% of ratios greater than 1), and acute dosing studies (0.01 – 178, weighted geometric mean 1.5, 55% of ratios greater than 1), suggesting that these differences in dosing are not the sole determinant of the increased incidence of early tumors, i.e., uncertainty and variability remain. Because these comparisons include different chemicals with different tissue specificities, it may be informative to consider liver as a target organ affected by all of these chemicals. The range of the magnitudes of the liver tumor incidence ratios of juvenile to adult exposures is similar for the repeated dosing studies (0.12 – 111, weighted geometric mean 41.8, 86% of ratios greater than 1, Table 4), lifetime dosing studies (0.47 – 79, weighted geometric mean 14.9, 80% of ratios greater than 1, Table 7), and acute dosing studies (0.1 – 40, weighted geometric mean 8.1, 77% of ratios greater than 1, Table 8). Thus, the repeated dose studies support the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action would lead to an increased tumor incidence compared with adult exposures of a similar duration and dose.

3.2.1.2. ***Acute Dosing Studies of Chemicals with a Mutagenic Mode of Action***

Acute dosing studies are available for eight carcinogens with a mutagenic mode of action that were administered to mice or rats [benzo[a]pyrene (BaP), dibenzanthracene (DBA), Diethylnitrosamine (DEN), dimethylbenzanthracene (DMBA), dimethylnitrosamine (DMN), ethylnitrosourea (ENU), methylnitrosourea (NMU), and urethane (also known as ethyl carbamate)] (Table 1b). Except for ENU and NMU, these compounds require metabolic activation to their active carcinogenic forms. These acute dosing studies generally compared a single exposure during the first few weeks of life with the identical or similar exposure in young adult animals (Tables 3 and 6). Many of these studies compared exposures during the preweaning period (i.e., approximately day 21 for rats and mice) with effects around week 6, which is approximately the age at which typical chronic bioassays begin dosing animals. These studies largely were by subcutaneous or ip injection, which historically have not been considered quantitatively relevant routes of environmental exposure for human cancer risk assessment by EPA. For purposes of comparing age-dependent susceptibilities to tumor development, these data are highly relevant. The injection route typically alters the pharmacokinetic time courses of the parent compound and the metabolites compared with oral or other exposures due to altered kinetics of absorption and metabolism. However, for these compounds and the systemic organ effects observed, there are several pharmacokinetic reasons to believe that the age-dependent trends would be similar with other routes of exposure. These compounds are expected to be reasonably well absorbed orally, comparable with injection routes, and largely require metabolic activation, so partial or complete absence of first pass metabolism in the injection studies would be similar to or underestimate metabolic activation when compared with oral exposure.

The early exposures often resulted in higher incidence of tumors than later exposures, with increased early susceptibilities up to 178-fold (unweighted ratios in Table 6 range from 0.011 to 178, with a weighted geometric mean of 1.5, and 55% of ratios greater than 1, Figure 2, Table 8). Examples of the general age-dependent decline in susceptibility of tumor response include BaP (liver tumors), DEN (liver tumors), ENU (liver and nervous system tumors), and urethane (liver and lung tumors). While generally the Day 1 and Day 15 time points were higher than later time points, in several cases similar tumor incidence was observed at both these early times (e.g., ENU-induced kidney tumors, Tables 6 and 8).

While the degree of susceptibility generally declines during the early postnatal period through puberty into early adulthood, there are exceptions due perhaps to pubertal periods of tissue development (e.g., mammary tissues) or very early development of xenobiotic metabolizing enzymes. One such exception was the increased incidence of mammary tumors in 5-8 week old rats given DMBA, compared with older or younger rats (Meranze et al., 1969; Russo et al., 1979). Meranze et al. (1969) reported 8% mammary tumors following a single dose of DMBA at less than two weeks, 56% if given once to animals between 5 and 8 weeks old, and 15% when given once to 26 week old rats. Thus, a ratio of 7.1 is obtained when comparing susceptibilities of 5–8 week and 26-week-old rats (Table 6) compared to a ratio of 0.2 when comparing the exposure at 2 weeks versus 26 weeks. A similar effect was observed by Russo et al. (1979); see Table 3. This observation corresponds well with pubertal development of the mammary tissue, with ovarian function commencing between 3 and 4 weeks (after the < 2 week time point in the Meranze et al., 1969 study), and mammary ductal growth and branching occurring such that it is approximately two-thirds complete by week 5, consistent with the 5–8 week susceptible period of Meranze et al. (Silberstein, 2001). While this differs from the general trend previously discussed, it indicates susceptibility later in the juvenile period rather than earlier. Another example of deviation from the general trend toward an age-dependent decline is DEN-induced lung tumors that were somewhat lower in incidence following exposure on day 1 than observed for the day 15 or day 42 exposures (Vesselinovitch et al., 1975) (Tables 3 and 6).

There are substantial differences in the early-life susceptibility of different tissues observed in the acute studies (Table 8). It should be noted that the target tissues vary with chemical, so the number of chemicals for which data are available varies for each tissue. Several tissues have weighted geometric mean ratios of greater than 1 including kidney, leukemia, liver, lymph, mammary, nerve, reticular tissue, thymic lymphoma, and uterus/vagina. Some of these, such as the nerve and mammary tumors, appear to have a very specific window of susceptibility, as noted above, and the ratios were much higher if the exposure occurred during this window. Tissues with weighted mean ratios less than 1 include forestomach, harderian gland, ovaries, and thyroid. Lung has a weighted geometric mean of 1. Many of the studies produced very high lung tumor responses regardless of age, so the results are difficult to interpret, as illustrated by the dose-response data with urethane in Rogers (1951) in which the increased early susceptibility is only apparent when the dose is low. The large numbers of studies with high lung tumor responses at all ages contribute to the differences in the weighted geometric means for the acute and for the repeated dosing studies.

Overall, the acute dosing studies support the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action would lead to an increased incidence of tumors compared with adult exposures of a similar dose and duration. These studies generally use the same dose and duration at all ages, and thus do not have the type of issues discussed for the repeated dosing studies. On the other hand, the acute dosing studies have limitations that were sufficient to decide that they should not be included in the quantitative adjustment of cancer potency. First, as mentioned in the previous paragraph, the large number of studies of lung tumors with almost 100% response observed at all doses and all ages would significantly bias the median ratio toward unity for a reason based on study design rather than biology. Second, cancer potency estimates are usually derived from chronic exposures. Therefore, any adjustment to those potencies should be, if possible, from similar exposures. Third, most exposures of concern to the Agency are from repeated or chronic exposures rather than acute exposures. Finally, many of the acute studies used ip exposures, which is not the usual route of exposure for environmental chemicals. Thus, the repeated and lifetime studies are more appropriate for the purpose of this analysis.

3.2.2. Carcinogens With Modes of Action Other Than Mutagenicity

Studies comparing tumors observed at the same sites following early postnatal and chronic adult exposures in a single protocol were available for six chemicals that do not act through a mutagenic mode of action [amitrole, dichlorodiphenyltrichloroethane (DDT), dieldrin, ethylene thiourea (ETU), diphenylhydantoin (DPH), polybrominated biphenyls (PBB)] (Table 5).

These chemicals cause tumors through several different, not necessarily well defined, modes of action. For example, thyroid hormone disruption by ETU causes thyroid tumors; some PBBs act through aryl hydrocarbon (Ah) receptors, while others are phenobarbital-like pleiotrophic inducers of liver enzymes and liver tumors. Three of these studies evaluated only mouse liver tumors (amitrole, DDT, dieldrin), while the other three evaluated a large number of tissues in both mice and rats (ETU, DPH, PBB). These studies generally included a combined perinatal and adult exposure as well as the separate perinatal or adult-only groups. It should be noted that no acute perinatal dosing studies of carcinogenesis were identified for these agents; such protocols are generally considered largely non-responsive for modes of action other than mutagenicity and potent estrogenicity (e.g., DES).

For five chemicals (amitrole, DDT, dieldrin, PBB and DPH), the same tumors were observed from early and/or adult exposures, though the studies for amitrole, DDT, and dieldrin only evaluates the animals for liver tumors. With ETU, no tumors in mice or rats were observed following perinatal exposure alone (except a small, not-statistically-significant increase in male rat thyroid tumors), while thyroid tumors were observed in adult rats and thyroid, liver, and pituitary tumors in adult mice. Analysis of the incidence of tumors per time of exposure shows early-lifestage susceptibilities. The range of the magnitudes of the tumor incidence ratios of juvenile to adult exposures is similar for the repeated dosing studies (0.06–13.3, weighted geometric mean 2.2, 27% of ratios greater than 1, Tables 5 and 8) and lifetime dosing studies (0.15–36, weighted geometric mean 3.4, 21% of ratios greater than 1, Tables 7 and 8). These ranges and means are similar to those for chemicals with a mutagenic mode of action, though the means and maximums are somewhat lower. Again, liver tumors are common to these chemicals. The range of the magnitudes of liver tumor incidence ratios of juvenile to adult exposures also is similar for the repeated dosing studies (0.06–13.3, weighted geometric mean 2.6, 43% of ratios greater than 1, Tables 5 and 8) and lifetime dosing studies (0.15–36, weighted geometric mean 5.8, 33% of ratios greater than 1, Tables 7 and 8).

The major factor that complicates the interpretation of the results is that these studies, except with DDT and dieldrin, involved dietary feeding initially to the mother, which potentially could increase or decrease the dose received by the pups. Due to the maternal dosing during pregnancy and lactation, the extent to which offspring received similar doses during different early and adult lifestages is particularly uncertain for DPH, ETU, and PBBs. Oral gavage doses in young animals were selected to approximate the average daily dose in adult dietary studies based on standard estimates of feed consumption in the studies with DDT and dieldrin, while the amitrole study involved dietary feeding postnatally to the mother so the young were dosed via lactation. In addition, DDT, dieldrin, and some PBBs are more persistent in the body than are most chemicals, leading to a prolonged exposure even following limited dosing. Thus, these studies provide evidence that early lifestages can be more susceptible to exposures to chemicals causing cancer through a variety of modes of action other than mutagenicity. However, the studies with ethylene thiourea, which acts via thyroid disruption, indicate that this is not necessarily the case for all modes of action.

3.2.3. Ionizing Radiation

As mentioned previously, the UNSCEAR, Annex I (2000) includes information derived from a wide range of both intentional (generally diagnostic or therapeutic medical) and accidental radiation exposures. Only information derived from the Japanese population (referred to as the Life Span Study in the UNSCEAR Annex I) is presented here. A statistically significant excess cancer mortality associated with radiation has been found among the bomb survivors for the following types of cancer: esophagus, stomach, colon, liver, lung, bone and connective tissue, skin, breast, urinary tract, and leukemia. Tables 9 and 10 are extracted from the tables in UNSCEAR, Annex I. The excess relative risk (ERR) is the increased cancer rate relative to an unexposed population; an ERR of 1 corresponds to a doubling of the cancer rate. Because of the low numbers of cancers in individual sites within narrow age groups, the ERRs for the various solid tumors and leukemia were presented only as less than or greater than 20 years of age at the time of exposure. The larger number of thyroid tumors enable a more detailed breakout shown in Table 10. Most sites show greater risks in the younger than in the older ages.

The U.S. EPA (1994) document presents a methodology for estimation of cancer risks in the U.S. population due to low-LET (linear energy transfer) radiation exposures using data from the Atomic Bomb Survivor Study (ABSS) as well as from selected medical exposures. The report developed mortality risk coefficients using several models that took into account age and gender dependence of dosimetry, radiogenic risk, and competing causes of death as well as transporting of risks across populations. The risk projections were updated using more recent vital statistics in a report that also included an uncertainty analysis (U.S. EPA, 1999). Details of the derivation of these coefficients are available at http://www.epa.gov/radiation/docs/rad_risk.pdf .

Table 11 contains the calculated age-specific risk coefficients derived from the application of the various models to the ABSS data. For most of the sites in the table, the risk coefficients are higher in the earlier age groups; liver, bone, skin, and kidney coefficients are age-independent and only esophageal cancer coefficients increase with increasing age. Also of note is that the coefficients generally are higher for females. Similar to the information from the UNSCEAR (2000) Annex, most sites show greater risks in the younger ages than the older ages.

However, a comparison of the two tables seems to show reversal of risks for some sites as a function of age at exposure. While the high sampling variability in the epidemiological data for some ages may contribute to this apparent reversal, the choice of risk models and associated parameters also is a factor.

4. DISCUSSION

The challenge for this analysis was how to use the existing, but limited, scientific database on early postnatal and juvenile exposures to carcinogens to inform a science policy decision on whether, and if so how, to assess the risk from childhood exposures to chemicals for which we have evidence of carcinogenicity only in adult humans or sexually mature laboratory animals. The database overall is of limited size (particularly compared with the number of chemicals that have been studied in adult occupational epidemiological studies or chronic bioassays). The majority of the human data involves exposures to ionizing radiation or DES (Anderson et al., 2000). More than 50 chemicals have been demonstrated to cause cancer following perinatal exposures in animals (without adult exposures), but only a subset of the chemicals have comparative studies across ages. The comparative experimental studies used 18 chemicals, 12 of which had mutagenic modes of action and 6 of which had data from repeated or lifetime exposures. Other analyses of similar data have found similar results (Hattis et al. 2005), but have focused on other aspects of the data, e.g., gender differences.

Previously published or internal U.S. EPA analyses have concluded that the standard animal bioassay protocols usually do not miss chemicals that would have been identified as carcinogens if perinatal exposures had been undertaken (McConnell, 1992; Miller et al., 2002; U.S. EPA, 1996). Given the increased complexity and costs of chronic bioassays with perinatal exposures, a limited number of such studies have been performed. However, these are the studies that largely constitute the available database for this analysis. In addition to the chronic bioassays with perinatal exposures, there are studies with acute dosing at different lifestages and a large number of studies with perinatal exposures without a directly comparative adult study.

Two other kinds of information can contribute toward developing a scientifically informed policy: theoretical analyses and analyses of stop studies.[4] Theoretical analyses suggest that the differential susceptibility would depend in part on the mode of action (i.e., at what step in the cancer process(s) the chemical was acting) and that the use of the average daily exposure prorated over a lifetime may underestimate or overestimate the cancer risk when exposures are time-dependent (Goddard and Krewski, 1995; Murdoch et al., 1992). Evidence for old-age-dependent promotion of basophilic foci in rats by peroxisome proliferators appears to provide a concrete example consistent with these theoretical analyses (Cattley et al., 1991; Kraupp-Grasl et al., 1991). The stop studies performed by the National Toxicology Program began exposure at the standard post-weaning age, but stopped exposure after varying periods of months. Other groups of animals were exposed for a full two years; all animals were evaluated

[4] Stop studies are studies in which exposure is halted after a predetermined period.

for tumors at the end of two years regardless of the duration of exposure (Halmes et al., 2000). Related data also are available from the stop studies with vinyl chloride (Drew et al., 1983). Analysis by Halmes et al. (2000) showed that, for six of the eleven chemicals and half the tumor sites, the assumption that the cancer risk would be equal when the product of concentration and time (i.e., C x T) was constant was incorrect, and usually underestimated risk, as more of the risk came from the beginning of the exposure rather than the end. This dependence of risk on both duration and intensity of exposure did not appear to be correlated with mutagenicity. It should be noted that these stop studies all involved exposures early in the life of the animal (as opposed to a limited number of cancer studies that looked at later periods of life; e.g., Drew et al., 1983), but the extent to which the differences in tumor outcome result from increased susceptibility in these early periods or the extended period for expression of the cancer cannot be evaluated. These stop studies also used doses as high as or higher than the highest dose used in the two-year exposure. This latter factor clearly had a significant effect for two chemicals, causing tumors at higher doses that were not observed at lower doses. These results suggest that pharmacokinetic or other dose-rate dependencies can make the effects of exposures at high doses different from those exposures at lower doses. While not directly informative about early childhood exposures, these studies provide a perspective on the common cancer risk assessment practice of averaging exposures over a lifetime, especially those that include earlier lifestages. Thus, alternative methods for estimating risks from short-term exposures during childhood should be considered.

Information on different lifestage susceptibilities to cancer risks for humans exists for ionizing radiation. The effects of chemical mutagens at different lifestages on cancer induction are derived from laboratory animal studies. While the induction of cancer by ionizing radiation and the induction of cancer by chemical mutagens are not identical processes, both involve direct damage to DNA as critical causal steps in the process. In both cases, the impacts of early exposure can be greater than the impacts of later exposures, probably due to some combination of early-lifestage susceptibility and the longer periods for observation of effects. As indicated in Tables 9 and 10, A-bomb survivors exhibited different lifestage dependencies at different tumor sites, though the total radiation-related incidence of tumors showed a general slow decline with age at exposure. However, as previously noted, there are apparent differences at some sites between the two tables. In addition to the sampling and modeling differences, the excess risk values in Table 9 are based on Japanese baselines while the coefficients in Table 10 reflect UNSCEAR's effort to transport the risks from the Japanese population to that of the United States. However, it is clear that the total radiation-related tumor incidence showed a general slow decline with age at exposure.

The studies in rodents of chemicals with mutagenic modes of action similarly support a general decline in induced cancer risk with age at exposure and similarly show some differences for individual tumor sites. In general, the earliest two or three postnatal weeks in mice and rats appeared to be the most susceptible, though some degree of increased susceptibility through puberty in rats (beginning around 5–7 weeks) and mice (beginning around 4–6 weeks) for some types of tumors exists.

All the acute dosing studies that demonstrated carcinogenicity with animals of different ages used chemicals with a mutagenic mode of action (Tables 4 and 6). These studies provide the clearest demonstrations of periods of differential susceptibility because the exposure rate is constant at the different ages. The repeated dose studies also include several of the most informative studies for assessing perinatal carcinogenesis, notably those on vinyl chloride and DEN (Tables 2 and 4). The vinyl chloride studies by Maltoni and colleagues are part of a large series of studies on this compound that included exposures to different concentrations for varying durations, including some at early lifestages (Maltoni et al., 1984). The DEN study by Peto et al. (1984) used a unique chronic study design in which groups of rats were exposed to multiple drinking water concentrations starting at 3, 6, or 20 weeks of life. This design provides information on the susceptibility of early exposure periods within a nearly lifetime exposure.

Beyond the analysis described here, there are conceptual biological rationales that would suggest DNA-damaging agents would have greater impacts on early lifestages. Growth involves substantial levels of cell replication, even in organs that in adults are only very slowly replicating, thus increasing the likelihood that a cell will undergo division before the DNA damage caused by the mutagen has been repaired. Increased replication also can lead to a greater division of initiated cells, leading to a larger number of initiated cells per specified dose. These periods of cell replication can vary for different tissues. For example, DMBA appears to be more effective at initiating mammary tumors in 6-8 week old rats, which are undergoing development of that tissue, than during earlier or later periods (Meranze et al., 1969). While tumor promotion processes can be very dependent upon the duration of promotion, initiation processes can occur in relatively brief periods (e.g., the single-dose studies in animals or radiation exposure in humans). Most tumors take extended periods to develop, making damage that occurs earlier in life more likely to result in tumors prior to death than would exposures that occur later in life. While some of these observations may also pertain to other modes, all of them (with some differences among tumor sites) appear to be potentially relevant to a greater susceptibility to mutagenic modes of action during early-life stages (vs. later-life stages).

The information on lifestage susceptibility for chemicals inducing cancers through modes of action other than direct DNA interaction is more varied, showing an increase in tumor incidence during perinatal exposure versus exposures of mature animals (e.g., polybrominated biphenyls induced liver tumors), no tumors from perinatal exposure (e.g., ethylene thiourea induced thyroid tumors), no effect of combined perinatal and adult exposure (e.g., DPH liver tumors in rats and female mice), and different tumors from perinatal exposure versus adult exposure (e.g., DES, ascorbate). These variations are likely a result of the modes of action of these chemicals and the pharmacokinetic differences in doses during different periods of life. No studies were evaluated that were directly comparable to the single-dose studies with mutagens, which clearly show significant differences in tumor responses after explicitly controlled doses at different lifestages.

Some evidence for an effect of early-lifestage exposures on tumor incidence was observed in studies with polybrominated biphenyls, amitrole, DDT, dieldrin, and diphenylhydantoin. These studies show increased incidence of tumors in mice from perinatal exposure, though only those for polybrominated biphenyls were statistically significant. (A nonstatistically significant increase also was observed in male rats with polybrominated biphenyls.) Combined perinatal and adult exposures generally gave statistically significant increases, though not necessarily for each sex and species (rat and mice) in the diphenylhydantoin and polybrominated biphenyl studies.

There are important demonstrations of chemicals acting through modes of action other than mutagenic to cause different tumor types with early-lifestage exposures compared with exposures for adults, e.g., tamoxifen and DES (Carthew et al., 2000; Carthew et al., 1996, Gass et al., 1964; Newbold et al., 1990, 1997, 1998). In addition, studies with *in utero* exposure to atrazine (Fenton and Davis, 2002), DES, and arsenic (Waalkes et al., 2003) indicate that early-life exposures to compounds can alter susceptibility of endocrine and reproductive organs. Three of these compounds (i.e., DES, genistein, and tamoxifen) bind to the estrogen receptor. Ongoing studies on ethinyl estradiol, nonylphenol, and genistein by the National Toxicology Program will add to this database for estrogens (Laurenzana et al., 2002; Newbold et al., 2001). These studies will evaluate cancer incidence in offspring exposed *in utero*, during lactation, and through adulthood via diet. A study with genistein found uterine tumor development to be dependent upon early-lifestage exposures (Newbold et al., 2001). Another recent study of estrogen found a shorter latency for mammary tumors in mice exposed at 8 and 12 weeks as compared to mice exposed at 4 or 18 weeks, indicating a susceptible period between 8 to 12 weeks of exposure (Yang, 2003). Thus, there is an actively growing database from which to consider issues of childhood exposure and cancer for compounds acting through the estrogen receptor or other mechanisms of endocrine disruption.

The ability to estimate with any accuracy the juvenile to adult cancer potency ratio depends very much on the experimental design used. The lifetime design has less ability to distinguish increased susceptibility from early-life exposure than the other types of designs. Consider two different experimental designs. In the first, the "lifetime" design, a group of animals are exposed starting as juveniles, and exposure continues through adulthood. A second group are exposed only in adulthood, and the juvenile:adult ratio results from a comparison of tumor incidences in the two groups. In the second, the "repeated" design, one group of animals is exposed only during the juvenile period, and is then followed through adulthood to assess tumor incidence, and a second group of animals is exposed only through adulthood. The lifetime design turns out to be a particularly insensitive design for estimating the juvenile:adult ratio.

The following example demonstrates the magnitude of the problem: Suppose the risk per day of exposure of a chemical is ten fold greater in the juvenile period as in the adult period, and animals exposed through adulthood at a particular dose level have an extra risk of 60% for having at least one tumor, while 1% of control animals have tumors. The adult exposure period is 94 weeks, while the juvenile exposure period is 4 weeks. Thus, in the lifetime design, the group of animals exposed as juveniles will receive a total of 98 weeks of exposure, (4 in juvenile and 94 in adult), while those receiving the adult-only exposure receive 94 weeks of exposure. In the repeated design, animals exposed as juveniles receive only 4 weeks of exposure, while the adults receive 94 weeks, just as in the lifetime design. Each group starts with 50 animals. Under these assumptions, using equations (1) and (2) from Section 2.3, the expected number of animals with tumors in the three treatment groups (control, juvenile-exposed, adult-exposed groups) in the two designs is:

	Number of animals with tumors		
	Control	**Early-life exposure**	**Adult exposure**
Lifetime	1	36	30
Repeated	1	16	30

Notice that in the "lifetime" design, only six more juvenile-exposed animals have tumors than in the adult-exposed group, whereas in the "repeated" design, 16 juvenile-exposed animals have tumors. The data in the lifetime design are consistent with the hypothesis of no tumors being induced during the juvenile period: the ratios 36/50 and 30/50 are not statistically significantly different. In other words, the data from the lifetime design are statistically consistent with the hypothesis of *no risk at all* during the juvenile period, even though the real response is a 10 times greater risk from early-life exposure. The difference between the results from the two different study designs is due to the one-hit model: each additional week of a long exposure contributes less than the previous week to the total number of animals with tumors.

Note that, even if the one-hit model is not correct, chronic exposure probably results in a non-statistically significant increase for the lifetime exposure including juveniles as compared with only adult exposure.

The proper measure of relative potency of an exposure in the juvenile period relative to an exposure in the adult period is the ratio of doses in the two periods that give the same incidence of tumors. However, most of the data sets used in this report contained only one non-control dose, precluding the extensive dose-response modeling that would be required to estimate this ratio of doses. However, this document largely considered chemicals for which a mutagenic mode of action has been established and for which a linear, no-threshold dose-response function is assumed for the low-dose range being considered for risk assessment. In the case of the linear dose-response function, the analysis of the relative response from the same dose will produce the same value as ratio of doses that produces the same incidence of tumors.

For a one-hit dose-response equation, the probability of developing a tumor after the same dose and duration in the juvenile or adult period is

$$P_a = 1 - (1 - P_0)e^{-m_a x}$$
$$P_j = 1 - (1 - P_0)e^{-m_j x}$$

for dose x. Suppose we want to calculate the dose D_a or D_j that results in a given incidence of tumors after an adult or juvenile exposure. From equation 1, D_a and D_j equal:

$$D_a = \frac{-\ln\left(\frac{1-P_c}{1-P_0}\right)}{m_a}$$
$$D_j = \frac{-\ln\left(\frac{1-P_c}{1-P_0}\right)}{m_j}$$

Thus, the ratio $D_a/D_j = m_j/m_a$, the ratio calculated in this document.

In summary, this analysis supports the conclusion that there can be greater susceptibility for the development of tumors as a result of exposures to chemicals acting through a mutagenic mode of action, when the exposures occur in early lifestages as compared with later lifestages. Thus, this Supplemental Guidance recommends for chemicals with a mutagenic mode of action for carcinogenesis when chemical-specific data on early-life exposure are absent, a default approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure. For chemicals acting through a non-mutagenic mode of action, e.g., hormonally mediated carcinogens, the available data suggest that other approaches may need to be developed for addressing cancer risk estimates from childhood exposures. This is a particular concern because the tumors arising from hormonally active chemicals appear to involve different sites when exposure is during early-life versus adulthood, an effect that has been observed relatively infrequently. Development of such approaches would require additional research to provide an expanded scientific basis for their support, including additional research and the possible development of new toxicity testing protocols that consider early lifestage dosing.

The current data do also not allow analysis of some issues of potential interest for risk assessment, e.g., potential increased risk of childhood cancer, from *in utero* or childhood exposures. Assessing the role of environmental exposures on childhood cancers is difficult, but additional research could include epidemiological studies or experimental studies with animals genetically designed to express cancers analogous to human childhood cancers. Rigorous quantification of exposure doses at different lifestages and in rodent pups in experimental studies would be useful for evaluating whether there is greater childhood susceptibility. Pharmacokinetic modeling could better define the internal doses to improve determination of the magnitude of increased susceptibility.

5. GUIDANCE FOR ASSESSING CANCER RISKS FROM EARLY-LIFE EXPOSURE

Consistent with the approach and recommendations of the U.S. EPA cancer risk assessment guidelines (U.S. EPA, 2004), any assessment of cancer susceptibility will begin with a critical analysis of the available information. Figure 3 shows the proposed steps in the process. The potential for increased susceptibility to cancer from early-life exposure, relative to comparable exposure later in life, generally warrants explicit consideration for each assessment.

When developing quantitative estimates of cancer risk, the Agency recommends integration of age-specific values for both exposure and toxicity/potency where such data are available and appropriate. Children, in general, are expected to have some exposures that differ from those of adults (either higher or lower), due to differences in size, physiology, and behavior. For example, children are generally assumed to eat more food and drink more water relative to their body weight than adults. Children's normal activities, such as putting their hands into their mouths or playing on the ground, can result in exposures to contaminants that adults do not encounter. Moreover, children and adults exposed to the same concentration of an agent in food, water, or air may receive different (higher or lower) internal doses due to differences, for example, in intake, metabolism, or absorption rates. Children are less likely than adults to be exposed to products typically used in industrial settings and often have more limited diets than adults. When assessing risks, if the data are available and relevant, it is important to include exposure that is measured or modeled for all lifestages, including exposures during childhood and during adulthood. EPA continues to develop better tools for assessing childhood exposure differences, such as the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002a), and models, such as Stochastic Human Exposure and Dose Simulation (SHEDS) and Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000; Zartarian et al., 2000)

Mode-of-action studies can be a source of data on quantitative differences between children and adults (Figure 3, Box 1). If the available information is sufficient to establish the agent's mode of action for early-life and adult exposures, then the implications for early-life exposure of that mode of action are used to develop separate risk estimates for childhood exposure. Pertinent information can be obtained both from agent-specific studies and from other studies that investigate the general properties of the particular mode of action. All data indicating quantitative differences between children and adults are considered in developing those portion(s) of the risk estimates for exposure estimates that include childhood exposure. Some examples include the potential for children to have a different internal dose of the active agent or a change in a key precursor event (see Section 2.4.3.4 of the *Guidelines for Cancer Risk Assessment*).

When the mode of action cannot be established (Figure 3, Box 2), the policy choice would be to use linear extrapolation to lower doses such that risk estimates are based on a lifetime average daily exposure without further adjustment. No general adjustment is recommended at this time. This policy choice is consistent with past U.S. EPA practice that has been favorably evaluated over the years. The result would be expected to produce plausible upper bound risk estimates, based on the use of linear extrapolation as a default in the absence of information on the likely shape of the dose-response curve.

When a mode of action other than mutagenicity is established, if it is nonlinear (Figure 3, Box 3) or linear (Figure 3, Box 4), no general adjustment is recommended at this time. Although the available studies (discussed previously) indicates that higher or lower cancer risks may result from early-life exposure, there is insufficient information or analyses currently available to determine a general adjustment at this time. As other modes of action become better understood, this information may include data on quantitative differences between children and adults. If such data are available, an analysis of the differences could be used to adjust risk estimates for childhood exposure. EPA expects to expand this Supplemental Guidance to specifically address modes of action other than mutagenicity when sufficient data are available and analyzed.

When the data indicate a mutagenic mode of action,[5] the available studies (discussed

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5 Determination of chemicals that are operating by a mutagenic mode of action entails evaluation of test results for genetic endpoints, metabolic profiles, physicochemical properties, and structure-activity analyses in a weight-of-evidence approach (Waters et al., 1999). Established protocols are used to generate the data (Cimino, 2001; OECD, 1998; U.S. EPA, 2002b); however, it is recognized that newer methods and technologies such as those arising from genomics can provide useful data and insights to a mutagenic mode of action. Carcinogens acting through a mutagenic mode of action generally interact with DNA and can produce such effects as DNA adducts and/or breakage. Carcinogens with a mutagenic mode of action often produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo,* which generally are supported by those performed *in vitro*. This mode of action is addressed in more detail in Section 2.3.5 of EPA's cancer guidelines (U.S. EPA, 2005).

above) indicate higher cancer risks resulting from a given exposure occurring early in life when compared with the same amount of exposure during adulthood. However, chemical-specific data relating to mode of action (e.g., toxicokinetic or toxicodynamic information) may suggest that even though a compound has a mutagenic mode of action, higher cancer risks may not result. Such data should be considered before applying the age-dependent adjustment factors.

If the available, chemical-specific information includes an epidemiologic study of the effects of childhood exposure or an animal bioassay involving early-life exposure (Figure 3, Box 5), then these studies are analyzed to develop risk estimates (i.e., cancer slope factors) that specifically address any potential for differential potency in early lifestages. An example is the IRIS assessment of vinyl chloride (U.S. EPA, 2000b; c).

In the absence of early-life studies on a specific chemical under consideration (Figure 3, Box 6), the extrapolation from the point of departure to lower doses employs linear extrapolation (see Section 3.3.1 of the U.S. EPA [2005] cancer guidelines). This choice is based on mode-of-action data indicating that mutagens can give rise to cancers with an apparently low-dose linear response. Adjustments to the resultant risk estimates are specified with regard to childhood exposures. This approach is adopted because risk estimates based on an average daily exposure prorated over a lifetime do not consider the potential for higher cancer risks from early-life exposure.

The adjustments described below reflect the potential for early-life exposure to make a greater contribution to cancers appearing later in life. The 10-fold adjustment represents an approximation of the weighted geometric mean tumor incidence ratio from juvenile or adult exposures in the repeated dosing studies (see Table 8). This adjustment is applied for the first 2 years of life, when toxicokinetic and toxicodynamic differences between children and adults are greatest (Ginsberg et al., 2002; Renwick, 1998). Toxicokinetic differences from adults, which are greatest at birth, resolve by approximately 6 months to 1 year, while higher growth rates extend for longer periods. The 3-fold adjustment represents an intermediate level of adjustment that is applied after 2 years of age through <16 years of age. This upper age limit represents middle adolescence following the period of rapid developmental changes in puberty and the conclusion of growth in body height in NHANES data (Hattis et al., 2005). Efforts to map the approximate start of mouse and rat bioassays (i.e., 60 days) to equivalent ages in humans ranged from 10.6 to 15.1 years (Hattis et al., 2005). Data are not available to calculate a specific dose-response adjustment factor for the 2 to <16-year age range, so EPA selected the 3-fold adjustment because it reflects a midpoint, i.e., approximately half the difference between 1 and 10 on a logarithmic scale ($10^{1/2}$), between the 10-fold adjustment for the first two years of life and no adjustment (i.e., 1-fold) for adult exposure. EPA also recognizes that exposures occurring near the end of life may have little effect on lifetime cancer risk, but lacks adequate data at present to provide an adjustment for this "wasted dose" effect. Similarly, since most of the studies involved only one latency period, the potential effect of early-life exposure on latency for the observed tumors could not be evaluated. The lack of data on effect on latency also limited the types of analyses that could be performed, e.g., more complex dose-response functions, such as multi-stage or clonal expansion models, could not be evaluated. Thus, the potential effects of early-life exposures on latency were not evaluated. Finally, as the adjustment factors are derived from a weighted geometric mean of the data evaluated, these adjustment will both over-estimate and under-estimate the potential potency for early-life exposure for chemicals with a mutagenic mode of action for carcinogenesis. An examination of the data in the tables demonstrates that some of the ratios were less than one, while others exceeded 10. For this reason, the Supplemental Guidance emphasizes that chemical-specific data should be used in preference to these default adjustment factors whenever such data are available.

The following adjustments represent a practical approach that reflects the results of the preceding analysis, which concluded that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life:

- For exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day of birth up until a child's second birthday), a 10-fold adjustment.

- For exposures between 2 and <16 years of age (i.e., spanning a 14-year time interval from a child's second birthday up until their sixteenth birthday), a 3-fold adjustment.

- For exposures after turning 16 years of age, no adjustment.

Clearly other age groups, such as an age group experiencing pubertal changes in physiology, or approximately ages 9 - 15, may experience changes in biological processes that could lead to modifications in the susceptibility to the effects of some carcinogens, depending on the mode of action. This Supplemental Guidance focuses on carcinogens with a mutagenic mode of action. For any mode of action, the Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework as described by EPA's cancer guidelines (U.S. EPA, 2005), is an appropriate mechanism for elucidating these lifestages. In general, the Agency's analyses of lifestages that may be susceptible will depend on three factors: (1) establishing the mode of action for carcinogenesis; (2) using knowledge about the biological and toxicological key events in that mode of action that are likely to be affected by lifestages; and (3) the availability, or development, of data that allow analysis of the effects of chemicals acting by that mode of action during the relevant ages. For each mode of action evaluated, therefore, the various age groupings determined to be at a differential risk, which may differ significantly from those proposed for the mutagenic mode of action, are expected to be evaluated independently of other modes of action. When data, including well established mode of action data, are available that allow specific evaluation of lifestage differences in toxicokinetics or toxicodynamics that would lead to lesser or greater susceptibility from early-life exposures to carcinogens, then those data should be used, as generally discussed in EPA's cancer guidelines (U.S. EPA, 2005), in preference to the default procedures described in this Supplemental Guidance.

The 10-fold and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. It is important to emphasize that these adjustments are combined with corresponding age-specific estimates of exposure to assess cancer risk. For example, for a 70-year lifetime, where there are data showing negligible exposure to children, the estimated cancer risk from childhood exposure would be also negligible and the lifetime cancer risk would be reduced to that resulting from the relevant number of years of adult exposure (in the absence of specific information, 55 years). Where there are data (measured or modeled) for childhood exposures, the age-group specific exposure values are used along with the corresponding adjustments to the slope factor. Where there are no relevant data or models for childhood exposures and only lifetime average exposure data are available, the lifetime exposure data are used with the adjustments to the slope factor for each age segment.

It is recognized that, when the exposure is fairly uniform over a lifetime, the effect of these adjustments on estimated lifetime cancer risk are small relative to the overall uncertainty of such estimates. These adjustments can be applied when estimating the cancer risk resulting from childhood exposure. These adjustments are applied when developing risk estimates from conventional animal bioassays or epidemiologic studies of effects of adult exposure. Some examples follow in the next section.

The Agency has also carefully considered both the advantages and disadvantages to extending the default potency adjustment factors to carcinogenic chemicals for which the mode of action remains unknown. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life susceptibility. At the present time, therefore, EPA is recommending these age-dependent adjustment factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and the above-mentioned science policy position. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a susceptible lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In this analysis, the data for non-mutagenic carcinogens, when the mode of action is unknown, were judged to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied.

6 COMBINING LIFESTAGE DIFFERENCES IN EXPOSURE AND DOSE-RESPONSE WHEN ASSESSING CARCINOGEN RISK - SOME EXAMPLES FOR CARCINOGENS THAT ACT THROUGH A MUTAGENIC MODE OF ACTION

It is important for the risk assessor to consider lifestage differences in both exposure and dose-response when assessing cancer risk resulting from early-life exposures. As discussed in Section 5, age dependent adjustments factors (ADAFs) in dose response (i.e., slope factors) are combined with age specific exposure estimates when assessing cancer risks. This is a departure from the way cancer risks have historically been based upon the premise that risk is proportional to the daily average of lifetime dose. This Supplemental Guidance recommends an integrative approach that can be used to assess total lifetime risk resulting from lifetime or less-than-lifetime exposure during a specific portion of a lifetime.

The following examples can help demonstrate how to apply this guidance by integrating potential lifestage differences in exposure and/or dose-response (potency), and also demonstrate what the resulting impacts are on calculated risks. These hypothetical examples consider risks from both lifetime, as well as less-than-lifetime oral exposures. Risks associated with inhalation exposure to carcinogens that act via a mutagenic mode of action are calculated in similar fashion by applying the appropriate ADAF(s) along with the corresponding inhalation unit risk estimate, using pertinent estimates of exposure concentration.

Note again, ADAFs are only to be used for agents with a mutagenic mode of action for carcinogenesis when chemical-specific data are absent. For all modes of action, when chemical-specific data are available for early-life exposure, those data should be used.

6.1 CALCULATING LIFETIME RISKS ASSOCIATED WITH LIFETIME EXPOSURES

Example 1: Consider a scenario of exposure to a carcinogen with a **nonmutagenic** mode of action. Suppose the oral cancer slope factor derived from a typical animal study (i.e., where dosing begins after puberty) is estimated to be 2 per mg/kg-d, and the exposure rate remains constant throughout life at 0.0001 mg/kg-d (this is equivalent to saying the daily average of lifetime dose rate is equal to 0.0001 mg/kg-d). The risk from lifetime exposure is calculated by multiplying the slope factor and the exposure rate:

$$\text{Risk} = (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d})$$

$= \quad 2 \times 10^{-4}$

Example 2: Now consider the same exposure scenario for a carcinogen with a **mutagenic** mode of action for which the oral cancer slope factor, derived from a typical animal study where dosing begins after puberty, is also estimated to be 2 per mg/kg-d. In this case, ADAFs are used, as follows.

a. To calculate lifetime risk for a population with average life expectancy of 70 years, sum the risk associated with each of the three relevant time periods:

- Risk during the first 2 years of life (where the ADAF = 10);
- Risk for ages 2 through < 16 (ADAF = 3); and
- Risk for ages 16 until 70 years (ADAF = 1).

Thus, risk equals the sum of:

- Risk for birth through < 2 yr = (2 per mg/kg-d) x 10 (ADAF) x (0.0001 mg/kg-d) x 2yr/70yr
  $= 0.6 \times 10^{-4}$
- Risk for ages 2 through < 16 = (2 per mg/kg-d) x 3 (ADAF) x (0.0001 mg/kg-d) x (13yr/70yr)
  $= 1.1 \times 10^{-4}$
- Risk for ages 16 until 70 = (2 per mg/kg-d) x 1 (ADAF) x (0.0001 mg/kg-d) x (55yr/70yr)
  $= 1.6 \times 10^{-4}$

Risk $= 0.6 \times 10^{-4} + 1.1 \times 10^{-4} + 1.6 \times 10^{-4}$
$= 3.3 \times 10^{-4}$

b. If exposure varies with age, then such differences are also included. Now suppose the same example as immediately above, except that exposure for ages 1 through <12 was twice as high as exposure for all other ages. In this case, sum the risk associated with each of the five relevant time periods in which exposure rates and/or potencies (slope factors) vary:

Risk equals the sum of:

- Risk for birth through < 1 yr (1yr) = (2 per mg/kg-d) x 10 (ADAF) x 0.0001 mg/kg-d x 1yr/70yr
  $= 0.3 \times 10^{-4}$
- Risk for ages 1 through < 2 (1yr) = (2 per mg/kg-d) x 10 (ADAF) x 0.0002 mg/kg-d x 1yr/70 yr
  $= 0.6 \times 10^{-4}$
- Risk for ages 2 through < 12 (10yr) = (2 per mg/kg-d) x 3 (ADAF) x 0.0002 mg/kg-d x 10yr/70yr
  $= 1.7 \times 10^{-4}$
- Risk for ages 12 through < 16 (4yr) = (2 per mg/kg-d) x 3 (ADAF) x 0.0001 mg/kg-d x 4yr/70yr
  $= 0.3 \times 10^{-4}$
- Risk for ages 16 until 70 years (55yr) = (2 per mg/kg-d) x 1 (ADAF) x 0.0001 mg/kg-d x 55yr/70yr
  $= 1.6 \times 10^{-4}$

Risk $= 0.3 \times 10^{-4} + 0.6 \times 10^{-4} + 1.7 \times 10^{-4} + 0.3 \times 10^{-4} + 1.6 \times 10^{-4}$
$= 4.5 \times 10^{-4}$

6.2 CALCULATING LIFETIME RISKS ASSOCIATED WITH LESS THAN LIFETIME EXPOSURES

If exposure only occurs for a limited number of years (for example, consider a family that lives near a source of exposure for a five-year period of time before moving away), it is critical to combine lifestage differences in exposure and dose-response for the relevant time interval. The examples presented below demonstrate how adjusting potency and/or exposure can affect the assessment of cancer risk.

Example 3: If exposure to a carcinogen with a mutagenic mode of action with an oral slope factor equal to 2 per mg/kg-d occurs during adulthood for only 5 years, the daily average of lifetime dose is time weighted to apportion risk for the number of years of exposure by a factor of 5/70:

Risk = (2 per mg/kg-d) x (0.0001 mg/kg-d) x (5yr/70yr)
= 1.4×10^{-5}

Example 4: If this 5-year exposure occurs during childhood, the risk calculations are adjusted to consider the potential for higher potency from early-life exposure. Assessors should remember that the age dependent adjustment factors for carcinogens with a mutagenic mode of action are applied only to exposure periods occurring up to age 16.

a. For a child exposed between ages 5 and 10, only a 3-fold ADAF is applied because the exposure occurs entirely between ages 2 and <16 years:

Risk = 3 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (5 yr/70 yr)
= 4.3×10^{-5}

b. For an exposure between ages 13 and <18, a 3-fold ADAF is applied only to the 3-year portion occurring before age 16:

Risk equals the sum of:

- Risk for ages 13 through < 16 (3yr) = 3 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (3 yr/70 yr)
= 2.6×10^{-5}
- Risk for ages 16 through < 18 (2yr) = 1 (ADAF) x (2 per mg/kg-d) x (0.0001 mg/kg-d) x (2 yr/70 yr)
= 0.6×10^{-5}

Risk = $2.6 \times 10^{-5} + 0.6 \times 10^{-5}$

$= 3.2 \times 10^{-5}$

c. For a child exposed from birth through age 5, different ADAFs are applied to the periods before and after age 2:

Risk equals the sum of:

- Risk for birth through < 2 (2yr) $= 10 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (2 \text{ yr}/70 \text{ yr})$
  $= 5.7 \times 10^{-5}$
- Risk for ages 2 through < 5 (3yr) $= 3 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (3 \text{ yr}/70 \text{ yr})$
  $= 2.6 \times 10^{-5}$

Risk $= 5.7 \times 10^{-5} + 2.6 \times 10^{-5}$
$= 8.3 \times 10^{-5}$

<u>Example 5</u>: Lifetime risk calculations based on less-than-lifetime exposure to a carcinogen with a mutagenic mode of action include any lifestage changes in potency as well as exposure. In this example, again consider a scenario of 5 years of exposure to a carcinogen with a mutagenic mode of action, but suppose that the exposure rate is found to vary from 0.0002 mg/kg-d during the first 2 years of life, to 0.0001 mg/kg-d during the last 3 years.

a. For a child exposed between birth and age 5, sum the risk associated with the two relevant time periods:

Risk equals the sum of:

- Risk for birth through < 2 (2yr) $= 10 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0002 \text{ mg/kg-d}) \times (2 \text{ yr}/70 \text{ yr})$

  $= 11.4 \times 10^{-5}$

- Risk for ages 2 through < 5 (3yr) $= 3 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (3 \text{ yr}/70 \text{ yr})$

  $= 2.6 \times 10^{-5}$

Risk $= 11.4 \times 10^{-5} + 2.6 \times 10^{-5}$

$= 1.4 \times 10^{-4}$

b. For comparison, a similar risk calculation for 5 years of exposure later in life (after age 16) in which the first 2 years of exposure are double that of the next 3 years are carried out without any adjustment for potency:

Risk equals the sum of:

- Risk for first 2 years of adult exposure $= 1 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0002 \text{ mg/kg-d}) \times (2\text{yr}/70\text{yr})$

  $= 1.1 \times 10^{-5}$

- Risk for final 3 years of adult exposure $= 1 \text{ (ADAF)} \times (2 \text{ per mg/kg-d}) \times (0.0001 \text{ mg/kg-d}) \times (3\text{yr}/70\text{yr})$

  $= 0.9 \times 10^{-5}$

Risk $= 1.1 \times 10^{-5} + 0.9 \times 10^{-5}$

$= 2 \times 10^{-5}$

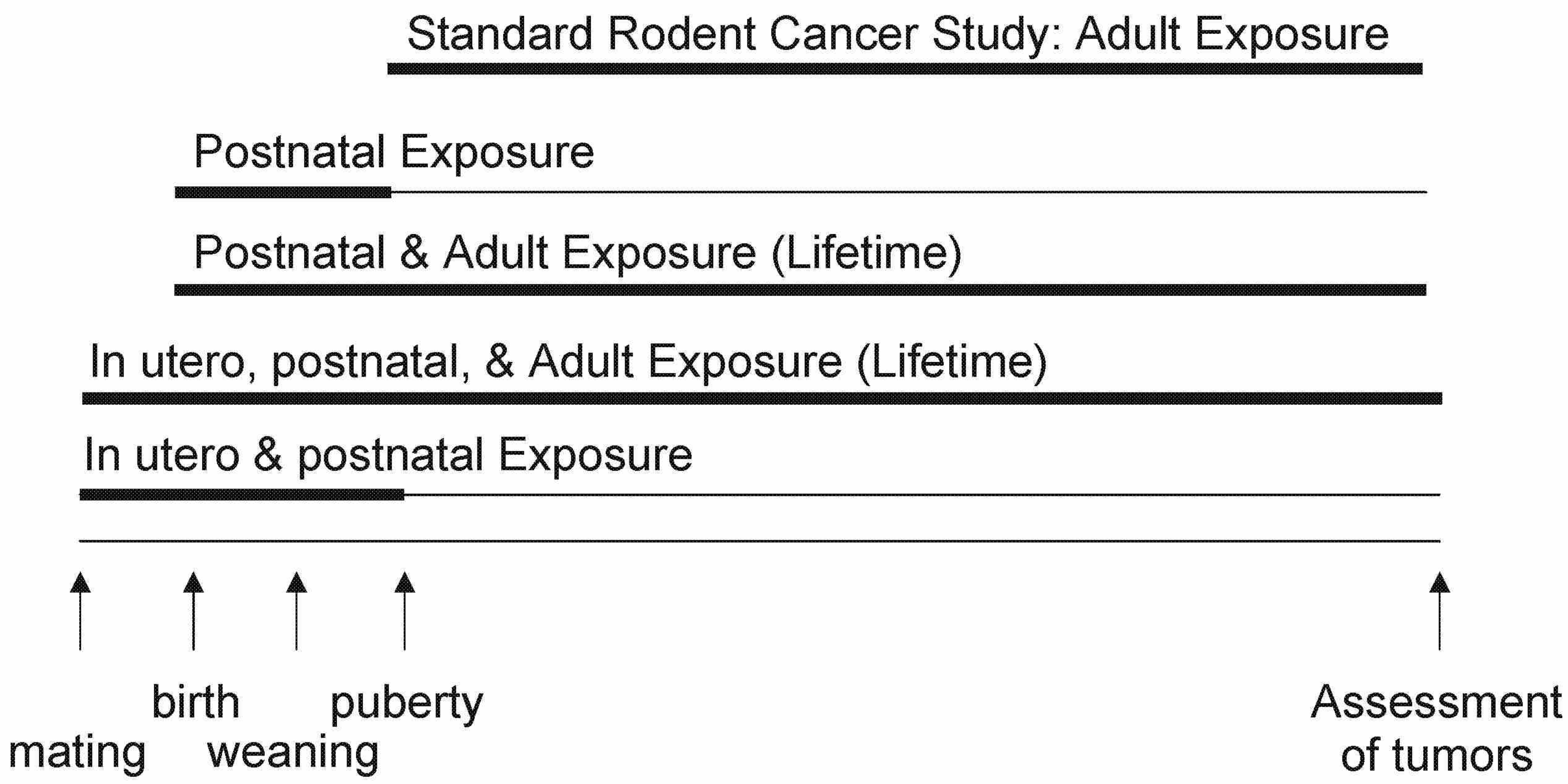

Figure 1. Study designs.

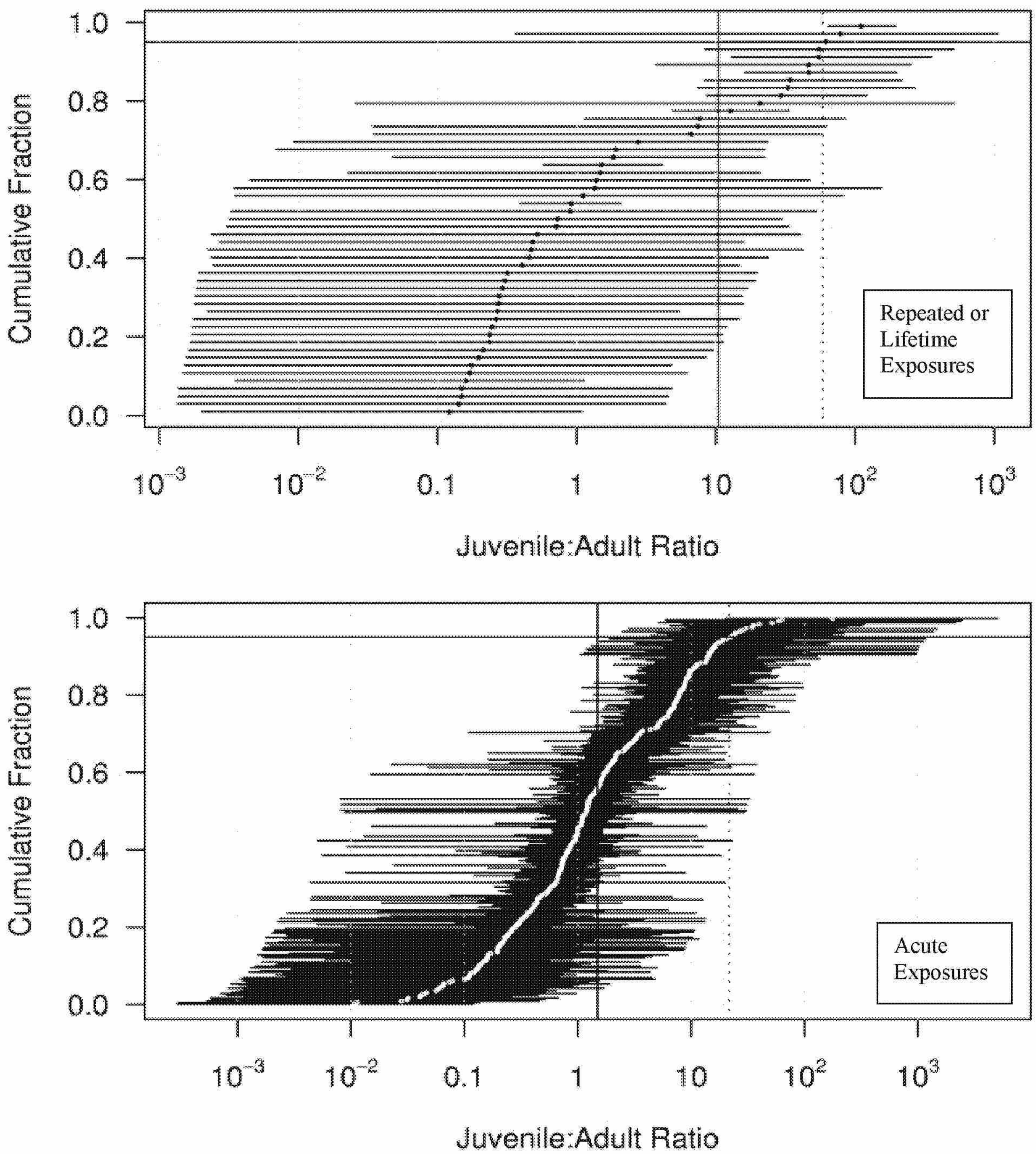

Figure 2: Posterior, unweighted geometric means and 95% confidence intervals for the ratios of juvenile to adult cancer potency for carcinogens acting primarily through a mutagenic mode of action. The top panel is for repeated and lifetime exposure studies (geometric mean in black), the bottom panel is for acute exposure studies mutagens (geometric mean in white). The horizontal lines to the left and right of each geometric mean correspond to 95% confidence limits. The vertical dark line represents the inverse-variance weighted geometric mean of the posterior geometric means. The horizontal dark line represents the 95th percentile of the unweighted distribution, with the vertical, dotted line establishing it value.

Figure 3. Flow chart for early-life risk assessment using mode of action framework

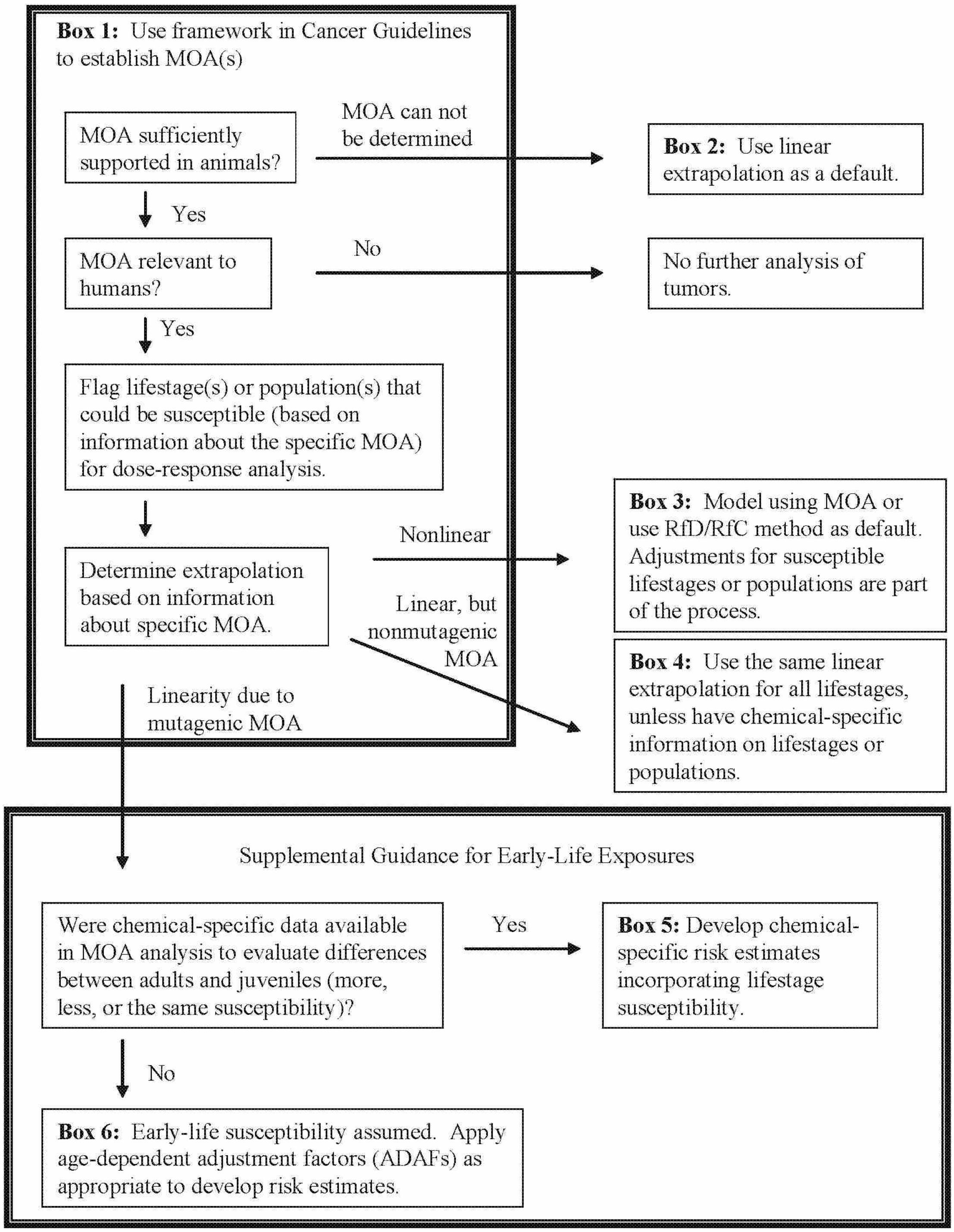

Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles

Chemical name	Review articles including prenatal and postnatal exposure					Chemicals selected for quantitative analysis
	Fujii (1991)	McClain et al. (2001)	Anderson et al. (2000)	Della Porta and Terracini (1969)	Other literature	
4-Acetylaminobiphenyl (AAB)	X					
4-Aminoazobenzene (AB)	X					
3-Amino-1,4,-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)	X					
2-Aminodipyridol[1,2-a:3',2'-d]imidazole (Glu-P-2)	X					
2-Amino-6-methyldipyridol[1,2-a:3',2'-d]imidazole (Glu-P-1)	X					
3-Amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2)	X					
Amitrole						X
Arsenic					X	
5-Azacytidine			X			
3'-Azido-3'-deoxythymidine (AZT)			X			
Azoxymethane			X			
Benz[*a*]anthracene				X		
Benzidine			X			X
Benzo[*a*]pyrene (BaP)	X			X		X
1-(4'Bromophenylazo)-1-phenyl-1-hydroperoxymethane (BPH)	X					
N-Butyl-N-(3-carboxypropyl)nitrosamine (BCPN)	X					
N-Butyl-N-(3 hydroxbutyl)nitrosamine (BBN)	X					
Butylnitrosourea (BNU)	X					
Cyclophosphamide		X				
Dibenz[*a,h*]anthracene (DBA)				X		X
Dibutylnitrosamine (DBN)	X					
Dichlorodiphenyltrichloroethane (DDT)						X
Dieldrin						X
2-Diethylaminoethyl-2,2-dephenylvalerate hydrochloride (SKF 525A)	X					

Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles (continued)

Chemical name	Review articles including prenatal and postnatal exposure					Chemicals selected for quantitative analysis
	Fujii (1991)	McClain et al. (2001)	Anderson et al. (2000)	Della Porta and Terracini (1969)	Other literature	
Diethylnitrosamine (DEN)	X		X			X
Diethylstilbesterol (DES)			X			
4-Dimethylaminoazobenzene				X		
1,2-Dimethylhydrazine (DMH)	X					
7,12-Dimethylbenz[*a*]anthracene (DMBA)	X		X	X		X
Dimethylnitrosamine (DMN)	X		X	X		X
5',5'-Diphenylhydantoin (DPH)						X
Estradiol	X	X				
6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (Santoquin)	X					
Ethylene thiourea (ETU)						X
Ethyl methane sulphonate				X		
Ethylnitrosobiuret			X			
Ethylnitrosourea (ENU)			X			X
N-2-Fluorenylacetamide (FAA)	X			X		
Genistein					X	
3-Hydroxyl-4-acetylaminobiphenyl (N-OH-AAB)	X					
N-2-Hydroxy-N-2-fluorenylacetamide (N-OH-FAA)	X					
2-Hydroxypropyl-propylnitrosamine			X			
9-Methylanthracene				X		
Methyl-2-benzylhydrazine			X			
Methylcholanthrene			X	X		
3-Methyl-4-dimethylaminoabenzene (3'ME-DAB)	X					
4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)			X			
Methylnitrosourea (NMU)			X			
Methylnitrosourethane			X			
1-Methyl-3-nitro-1-nitrosoguanidine (MNNG)	X					

Table 1a. Chemicals that have been found to have carcinogenic effects from prenatal or postnatal exposure in animals as identified in different review articles (continued)

Chemical name	Review articles including prenatal and postnatal exposure					Chemicals selected for quantitative analysis
	Fujii (1991)	McClain et al. (2001)	Anderson et al. (2000)	Della Porta and Terracini (1969)	Other literature	
2-Naphthylamine				X		
2-Naphthylhydroxyamine				X		
Nickel acetate			X			
N-Nitrosobuylamine			X			
4-Nitroquinoline-1-oxide			X	X		
N-Nitrosomethyl(2-oxopropyl)amine			X			
2-Oxopropyl-propylnitrosamine			X			
1-Phenyl-3,3',-dimethylhydrzine			X			
1-Phenyl-3,3,-dimethyltriazene			X			
Polybrominated biphenyls (PBBs)						X
Safrole (3,4-methylenedioxyally benzene)	X		X			X
Soot	X					
Sterigmatocystin	X					
Tamoxifen					X	
1,3,5-Trimethyl-2,4,6-tris[3,5-di-tert-butyl-4-hydroxybenzyl]benzene (Ionox 33)	X					
Urethane (ethyl carbamate)			X	X		X
Vinyl chloride						X

Table 1b. List of chemicals considered in this analysis. (These are chemicals for which both early-life and adult exposure are reported in the same animal experiment.)

Chemical	References	Study type	Mutagenic mode of action
Amitrole	Vesselinovitch (1983)	Repeat dosing	
Benzidine	Vesselinovitch et al. (1975b)	Repeat dosing	X
Benzo[*a*]pyrene (BaP)	Vesselinovitch et al. (1975a)	Acute exposure	X
Dibenzanthracene (DBA)	Law (1940)	Acute exposure	X
Dichlorodiphenyltrichloroethane (DDT)	Vesselinovitch et al. (1979)	Repeat dosing Lifetime exposure	
Dieldrin	Vesselinovitch et al. (1979)	Repeat dosing Lifetime exposure	
Diethylnitrosamine (DEN)	Peto et al. (1984)	Lifetime exposure	X
	Vesselinovitch et al. (1984)	Acute exposure	
Dimethylbenz[*a*]anthracene (DMBA)	Meranze et al. (1969)	Acute exposure	X
	Pietra et al. (1961)	Acute exposure	
	Walters (1966)	Acute exposure	
Dimethylnitrosamine (DMN)	Hard (1979)	Acute exposure	X
Diphenylhydantoin, 5,5- (DPH)	Chhabra et al. (1993b)	Repeat dosing Lifetime exposure	
Ethylnitrosourea (ENU)	Naito et al. (1981)	Acute exposure	X
	Vesselinovitch et al. (1974)	Acute exposure	
	Vesselinovitch (1983)	Acute exposure	
Ethylene thiourea (ETU)	Chhabra et al. (1992)	Repeat dosing Lifetime exposure	
3-Methylcholanthrene (3-MU)[a]	Klein (1959)	Repeat dosing	X
Methylnitrosourea (NMU)	Terracini and Testa (1970) Terracini et al. (1976)	Acute exposure Acute exposure	X
Polybrominated biphenyls (PBBs)	Chhabra et al. (1993a)	Repeat dosing Lifetime exposure	
Safrole	Vesselinovitch et al. (1979)	Repeat dosing Lifetime exposure	X
Urethane	Chieco-Bianchi et al. (1963) Choudari Kommineni et al. (1970) De Benedictis et al. (1962) Fiore-Donati et al. (1962)	Acute exposure Acute exposure Acute exposure Acute exposure	X
	Klein (1966)	Acute exposure Lifetime exposure	
	Liebelt et al. (1964)	Acute exposure	
	Rogers (1951)	Acute exposure	
Vinyl chloride (VC)	Maltoni et al. (1984)	Repeat dosing	X

[a] Formerly known as 20-methylcholanthrene.

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
Amitrole	Mice ($B6C3F_1$)	liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/98 (1%)	0/96 (0%)	Incidences are mice with adenomas or carcinomas.	Vesselinovitch (1983)
			Gestation day 12	Diet, to mothers	500 ppm	Gestation day 12 to delivery		6/74 (8%)[b]	0/83 (0%)[b]		
			Newborn	Diet, to mothers	500 ppm	Birth until weaning		10/45 (22%)[b]	0/55 (0%)[b]		
			At weaning	Diet, to offspring	500 ppm	From weaning to 90 weeks		20/55 (36%)[b]	9/49 (18%)[b]		
Benzidine	Mice ($B6C3F_1$)	liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/98 (1%)	0/100 (0%)	Higher sensitivity in males during perinatal period, in females during adulthood. Incidences are mice with adenomas or carcinomas.	Vesselinovitch et al. (1975b) Vesselinovitch et al. (1979a)
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 to delivery		17/55 (31%)[c]	2/62 (3%)[d]		
			Newborn	Diet, to mothers	150 ppm	Birth until weaning		62/65 (95%)[c]	2/43 (5%)[d]		
			At weaning	Diet, to offspring	150 ppm	From weaning to 90 weeks		22/50 (44%)[c]	47/50 (94%)[c]		
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 until weaning		49/49 (100%)[c]	12/48 (25%)[c]		
			Gestation day 12	Diet, to mothers	150 ppm	Gestation day 12 until 90 weeks		50/50 (100%)[c]	47/50 (94%)[c]		
DDT Dichlorodiphenyl-trichloroethane	Mice ($B6C3F_1$)	liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/50 (2%)	—		Vesselinovitch et al. (1979b)
			Week 1	Gavage, daily	230 µg	Weeks 1–4		5/49 (10%)[d]	—		
			Week 5	Diet, daily	150 ppm	Weeks 5–90		8/49 (16%)[d]	—		
			Week 1	Gavage, daily until 4 weeks, then in diet	230 µg 150 ppm (diet)	Weeks 1–90		10/50 (20%)[c]	—		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
Dieldrin	Mice ($B6C3F_1$)	liver	Control	None	Control: 0 ppm	N/A	90 weeks	1/58 (2%)	—		Vesselinovitch et al. (1979b)
			Week 1	Gavage, daily	12.5 µg	Weeks 1–4		3/46 (7%)[b]	—		
			Week 5	Diet, daily	10 ppm	Weeks 5–90		7/60 (12%)[b]	—		
			Week 1	Gavage, daily until 4 weeks, then in diet	12.5 µg 10 ppm	Weeks 1–90		21/70 (30%)[a]	—		
DEN[e] Diethylnitrosamine	Rats (Colworth)	liver	Control		Control	N/A		29/384 (8%)		Highest tumor rate when dosed at earlier ages. Incidents are rats with adenomas or carcinomas.	Peto et al. (1984)
			Week 3	Diet (in drinking water), daily	16 different doses combined[f]	From week 3 until death	6 months–3 years	105/180 (58%)[b]			
			Week 6			From week 6 until death		714/1440 (50%)[b]			
			Week 20			From week 20 until death		76/180 (42%)[b]			
		esophagus	Control		Control	N/A		0/384 (0%)			
			Week 3	Diet (in drinking water), daily	16 different doses combined[g]	From week 3 until death		77/180 (43%)[b]			
			Week 6			From week 6 until death		663/1440 (46%)[b]			
			Week 20			From week 20 until death		88/180 (49%)[b]			

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DPH Diphenylhydantoin, 5,5-	Rats (F344/N)	liver	Control	Control	0 ppm	N/A	2 years	0/50 (0%)	0/50 (0%)	In rats, perinatal exposure ranged from 63 to 630 ppm, and adult exposures ranged from 240 to 2,400 ppm. In mice, perinatal exposure ranged from 21 to 210 ppm. Adult exposure ranged from 30 to 300 ppm in males and 60 to 600 ppm in females. Tumor incidences are animals with adenomas or carcinomas.	Chhabra et al. (1993b)
			Perinatal	Diet, daily	630 ppm	Perinatal through 8 weeks		1/50 (2%)[d]	0/49 (0%)[d]		
			8 weeks		800 ppm	8 weeks–2 years		2/50 (4%)[d]	1/50 (2%)[d]		
			8 weeks		2,400 ppm	8 weeks–2 years		4/50 (8%)[d]	1/50 (2%)[d]		
			Perinatal		630–800	Perinatal through 2 years		1/49 (2%)[d]	0/50 (0%)[d]		
			Perinatal		630–2,400 ppm	Perinatal through 2 years		5/49 (10%)[c]	0/50 (0%)[d]		
	Mice ($B6C3F_1$)	liver	Control	Control male	0 ppm	N/A	2 years	29/50 (58%)			
			Perinatal	Diet, male	210 ppm	Perinatal through 8 weeks		33/50 (66%)[d]			
			8 weeks		100 ppm	8 weeks–2 years		29/49 (59%)[d]			
			8 weeks		300 ppm	8 weeks–2 years		26/49 (53%)[d]			
			Perinatal		210–100 ppm	Perinatal through 2 years		35/49 (71%)[d]			
			Perinatal		210–300 ppm	Perinatal through 2 years		41/50 (82%)[c]			
			Control	Control female	0 ppm	N/A	2 years		5/48 (10.4%)[d]		
			Perinatal	Diet, female	210 ppm	Perinatal through 8 weeks			12/49 (24.5%)[d]		
			8 weeks		200 ppm	8 weeks–2 years			14/49 (28%)[c]		
			8 weeks		600 ppm	8 weeks–2 years			30/50 (60%)[c]		
			Perinatal		210–200 ppm	Perinatal through 2 years			16/50 (32%)[c]		
			Perinatal		210–600 ppm	Perinatal through 2 years			34/50 (68%)[c]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
ETU Ethylene thiourea	Rats (F344/N)	thyroid	Control	Control	0 ppm	N/A	2 years	1/49 (2%)	3/50 (6%)	Tumor incidences are animals with adenomas or carcinomas.	Chhabra et al. (1992)
			Perinatal	Diet, daily	90 ppm	Perinatal through 8 weeks		4/49 (8%)[d]	3/50 (6%)[d]		
			8 weeks		83 ppm	8 weeks–2 years		12/46 (26%)[c]	7/44 (16%)[d]		
			8 weeks		250 ppm	8 weeks–2 years		37/50 (74%)[c]	30/49 (61%)[c]		
			Perinatal		90–83 ppm	Perinatal through 2 years		13/50 (26%)[c]	9/47 (19%)[d]		
			Perinatal		90–250 ppm	Perinatal through 2 years		48/50 (96%)	37/50 (74%)		
	Mice (B6C3F$_1$)	liver	Control	Control	0 ppm	N/A	2 years	20/49 (41%)	4/50 (8%)		
			Perinatal	Diet, daily	330 ppm	Perinatal through 8 weeks		13/49 (26.5%)[d]	5/49 (10%)[d]		
			8 weeks		330 ppm	8 weeks–2 years		32/50 (64%)[c]	44/50 (88%)[c]		
			8 weeks		1,000 ppm	8 weeks–2 years		46/50 (92%)[c]	48/50 (96%)[c]		
			Perinatal		330–330 ppm	Perinatal through 2 years		34/49 (69%)[c]	46/50 (92%)[c]		
			Perinatal		330–1,000 ppm	Perinatal through 2 years		47/49 (6%)[c]	49/50 (98%)[c]		
		thyroid	Control	Control	0 ppm	N/A		1/50 (2%)	0/50 (0%)		
			Perinatal	Diet, daily	330 ppm	Perinatal through 8 weeks		1/46 (2%)[d]	1/49 (2%)[d]		
			8 weeks		330 ppm	8 weeks–2 years		1/49 (2%)[d]	2/50 (4%)[d]		
			8 weeks		1,000 ppm	8 weeks–2 years		29/50 (58%)[c]	38/50 (76%)[c]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
ETU Ethylene thiourea (continued)			Perinatal		330–330 ppm	Perinatal through 2 years		2/48 (4%)[d]	10/49 (20%)[c]		
			Perinatal		330–1,000 ppm	Perinatal through 2 years		35/49 (71%)[c]	38/50 (76%)[c]		
		pituitary	Control	Control	0 ppm	N/A		0/44 (0%)	11/47 (23%)		
			Perinatal	Diet, daily	330 ppm	Perinatal through 8 weeks		0/42 (0%)[d]	11/48 (23%)[d]		
			8 weeks		330 ppm	8 weeks–2 years		0/42 (0%)[d]	19/49 (39%)[d]		
			8 weeks		1,000 ppm	8 weeks–2 years		8/41 (19.5%)[c]	26/49 (53%)[c]		
			Perinatal		330–330 ppm	Perinatal through 2 years		0/45 (0%)[d]	26/47 (55%)[c]		
			Perinatal		330–1,000 ppm	Perinatal through 2 years		4/39 (10%)[d]	24/47 (51%)[c]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death		Tumor incidence		Reference
							M	F	M	F	
3-Methylcholanthrene (formerly known as 20-methylcholanthrene)	Mice (Albino)	liver	Control	gavage, 3× per week	NA	NA	475 days	480 days	3/39 (7.7%)	0/36 (0%)	Klein (1959)
			8 days		0.25 mg/g	10×	311 days	321 days	21/25 (84%)[b]	7/30 (23.3%)[b]	
			90 days		0.25 mg/g	10×	330 days	366 days	1/26 (3.8%)[b]	0/29 (0%)[d]	
		lung	Control		NA	NA	475 days	480 days	17/39 (43.6%)	14/36 (38.9%)	
			8 days		0.25 mg/g	10×	311 days	321 days	25/25 (100%)[b]	28/30 (93.3%)[b]	
			90 days		0.25 mg/g	10×	330 days	366 days	25/26 (96.2%)[b]	27/29 (93.1%)[b]	
		fore-stomach	Control		NA	NA	475 days	480 days	0/39 (0%)	0/36 (0%)	
			8 days		0.25 mg/g	10×	311 days	321 days	12/25 (48%)[b]	12/30 (40%)[b]	
			90 days		0.25 mg/g	10×	330 days	366 days	13/26 (50%)[b]	8/29 (27.6%)[b]	
		skin	Control		NA	NA	475 days	480 days	0/39 (0%)	0/36 (0%)	
			8 days		0.25 mg/g	10×	311 days	321 days	4/25 (16%)[b]	4/30 (13.3%)[b]	
			90 days		0.25 mg/g	10×	330 days	366 days	1/26 (3.8%)[b]	1/25 (4%)[b]	

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
PBBs Polybrominated biphenyls	Rats (F344/N)	liver[g]	Control	Control	0 ppm	N/A	2 years	1/50 (2%)	0/50 (0%)	Findings suggest that combined perinatal and adult exposure increases PBB-related hepatocellular carcinogenicity relative to adult-only exposure in mice and female rats. Apparent association between increasing incidences of MCL and exposure to PBB in male and female rats. Tumor incidences are animals with adenomas or carcinomas.	Chhabra et al. (1993a)
			Perinatal	Diet	10 ppm	Perinatal–8 weeks		5/50 (10%)[d]	0/50 (0%)[d]		
			8 weeks		10 ppm	8 weeks–2 years		12/49 (24%)[c]	12/50 (24%)[c]		
			8 weeks		30 ppm	8 weeks–2 years		41/50 (82%)[c]	39/50 (78%)[c]		
			Perinatal		10–10 ppm	Perinatal–2 years		16/50 (32%)[c]	39/50 (78%)[c]		
			Perinatal		10–30 ppm	Perinatal–2 years		41/50 (82%)[c]	47/50 (94%)[c]		
		Mono-nuclear cell leukemia (MCL)	Control	Control	0 ppm	N/A	2 years	25/50 (50%)	14/50 (28%)		
			Perinatal	Diet	10 ppm	Perinatal–8 weeks		31/50 (62%)[d]	13/50 (26%)[d]		
			8 weeks		10 ppm	8 weeks–2 years		33/50 (66%)[c]	22/50 (44%)[d]		
			8 weeks		30 ppm	8 weeks–2 years		31/50 (62%)[d]	23/50 (46%)[c]		
			Perinatal		10–10 ppm	Perinatal–2 years		37/50 (74%)[c]	27/50 (54%)[c]		
			Perinatal		10–30 ppm	Perinatal–2 years		37/50 (74%)[c]	25/50 (50%)[c]		
	Mice ($B6C3F_1$)	liver[g]	Control	Control	0 ppm	N/A	2 years	16/50 (32%)	5/50 (10%)		
			Perinatal	Diet	30 ppm	Perinatal–8 weeks		40/50 (80%)[c]	21/50 (42%)[c]		
			8 weeks		10 ppm	8 weeks–2 years		48/49 (98%)[c]	42/50 (84%)[c]		
			8 weeks		30 ppm	8 weeks–2 years		48/50 (96%)[c]	47/48 (98%)[c]		
			Perinatal		10 ppm	Perinatal–2 years		46/49 (94%)[c]	44/50 (88%)[c]		
			Perinatal		30–30 ppm	Perinatal–2 years		50/50 (100%)[c]	47/47 (100%)[c]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
Safrole	Mice ($B6C3F_1$)	liver	Control	None	None	N/A	90 weeks	3/100 (3%)	0/100 (0%)	Highest tumor rate in males due to preweaning treatment.	Vesselinovitch et al. (1979b)
			Day 12 of gestation	Gavage, to mothers	120 µg/g body weight	4× (days 12, 14, 16, 18)		2/61 (3%)[d]	0/65 (0%)[d]		
			Newborn	Gavage, to mothers, on alternate days	120 µg/g body weight	From birth until weaning		28/83 (34%)[c]	2/80 (3%)[d]	Highest tumor rate in females due to susceptibility in adulthood.	
			At weaning	Gavage, to offspring, 2× weekly	120 µg/g body weight	From weaning until 90 weeks		4/35 (11%)[d]	22/36 (61%)[c]	Tumor incidences are mice with adenomas or carcinomas.	
			Day 12 of gestation	Gavage, to mothers, alternate days	120 µg/g body weight	From gestation until weaning		22/68 (32%)[b]	1/72 (1%)[b]		
			Day 12 of gestation	Gavage, to mothers, alternate days until weaning; Gavage, to offspring, 2× weekly	120 µg/g body weight	From gestation until 90 weeks		19/37 (51%)[b]	37/46 (80%)[b]		
Urethane	Mice ($B6AF_1/J$)	liver	1 week	gavage	2.5 mg/pup	1×	39–40 weeks	**Tumor incidence[a]**		No tumor data for controls.	Klein (1966)
								M	**F**		
								12/37 (33%)[b]	0/40 (0%)[b]		
			1 week		2.5 mg/pup	16× (1× at 1 week; 3× weekly for 5 weeks beginning at 4 wks of age)	39 weeks	11/33 (33%)[b]	0/31 (0%)[b]		
			4 weeks		2.5 mg/pup	15× (3× weekly for 5 weeks beginning at 4 weeks of age)	41 weeks	0/37 (0%)[b]	0/31 (0%)[b]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
VC Vinyl chloride	Rats (Sprague-Dawley)	liver angio-sarcoma	Control	Control	0 ppm	N/A	135 weeks	0/22 (0%)	0/29 (0%)	Higher tumor risk when exposed at birth, higher for females.	Maltoni et al. (1984)
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	5/18 (28%)[b]	12/24 (50%)[b]		
					10,000 ppm			6/24 (25%)[b]	9/20 (45%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	3/17 (18%)[b]	10/25 (40%)[b]		
					10,000 ppm			3/21 (14%)[b]	4/25 (16%)[b]		
		zymbal gland	Control	Control	0 ppm	N/A	135 weeks	0/28 (0%)	0/29 (0%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	1/12 (8%)[b]	1/17 (6%)[b]		
					10,000 ppm			1/17 (6%)[b]	0/17 (0%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	3/29 (10%)[b]	4/30 (13%)[b]		
					10,000 ppm			10/30 (33%)[b]	6/30 (20%)[b]		
		leukemia	Control	Control	0 ppm	N/A	135 weeks	0/27 (0%)	1/29 (3%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	N/A	1/7 (14%)[b]		
					10,000 ppm			2/6 (33%)[b]	0/15 (0%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	N/A	0/29 (0%)[b]		
					10,000 ppm			0/27 (0%)[b]	2/29 (7%)[b]		
		nephro-blastoma	Control	Control	0 ppm	N/A	135 weeks	0/22 (0%)	0/29 (0%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	0/15 (0%)[b]	0/21 (0%)[b]		
					10,000 ppm			0/19 (0%)[b]	0/17 (0%)[b]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
VC Vinyl chloride (continued)			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	4/18 (22%)[b]	1/26 (4%)[b]		
					10,000 ppm			3/21 (14%)[b]	2/25 (8%)[b]		
		angio-sarcomas: other sites	Control	Control	0 ppm	N/A	135 weeks	0/29 (0%)	0/29 (0%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	1/15 (7%)[b]	0/21 (0%)[b]		
					10,000 ppm			0/19 (0%)	0/17 (0%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	1/29 (3%)[b]	2/30 (7%)[b]		
					10,000 ppm			2/30 (7%)[b]	1/30 (3%)[b]		
		angiomas and fibromas: other sites	Control	Control	0 ppm	N/A	135 weeks	0/28 (0%)	2/29 (7%)[b]		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	1/15 (7%)[b]	0/21 (0%)[b]		
					10,000 ppm			2/19 (11%)[b]	1/17 (6%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	2/29 (7%)[b]	2/30 (7%)[b]		
					10,000 ppm			2/29 (7%)[b]	1/29 (3%)[b]		
		hepatoma	Control	Control	0 ppm	N/A	135 weeks	0/19 (0%)	0/28 (0%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	9/18 (50%)[b]	11/24 (46%)[b]		
					10,000 ppm			13/24 (54%)[b]	7/20 (35%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	0/10 (0%)[b]	1/17 (6%)[b]		
					10,000 ppm			1/8 (13%)[b]	0/16 (0%)[b]		

Table 2. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult repeated exposures (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
VC Vinyl chloride (continued)		skin carcinomas	Control	Control	0 ppm	N/A	135 weeks	0/20 (0%)	1/29 (3%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	1/10 (10%)[b]	1/14 (7%)[b]		
					10,000 ppm			1/16 (6%)[b]	0/15 (0%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	0/15 (0%)[b]	2/19 (11%)[b]		
					10,000 ppm			2/13 (15%)[b]	1/21 (5%)[b]		
		neuro-blastoma	Control	Control	0 ppm	N/A	135 weeks	0/22 (0%)	0/29 (0%)		
			Newborn	Inhalation	6,000 ppm	4 hrs/day, 5 days/wk, 5 weeks	124 weeks	0/18 (0%)[b]	0/29 (0%)[b]		
					10,000 ppm			0/22 (0%)[b]	0/19 (0%)[b]		
			Week 13		6,000 ppm	4 hrs/day, 5 days/wk, 52 weeks	135 weeks	2/21 (10%)[b]	1/27 (4%)[b]		
					10,000 ppm			2/22 (9%)[b]	5/26 (19%)[b]		

[a] Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.
[b] Not evaluated by authors.
[c] Significant compared with controls.
[d] Evaluated but not significant compared with controls.
[e] Reported as NDEA (N-nitrosodiethylamine) in the original document.
[f] Results from each dose are not available.
[g] Tumors were adenomas or carcinomas.

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
BaP Benzo[*a*]pyrene	Mice ($B6C3F_1$)	liver	Control	Control	None	N/A	142 weeks	7/100 (7%)	1/100 (1%)	In general, hepatomas developed with significantly higher incidence (p<0.01) in mice that were treated within 24 hours of birth or at 15 days of age than they did in similarly treated animals at 42 days of age. + higher for males.	Vesselinovitch et al. (1975a)
			Day 1	i.p.	75 µg/g body weight	1×	86 weeks (m) 129 weeks (f)	26/47 (55%)[b]	3/45 (7%)[b]		
					150 µg/g body weight	1×	81 weeks (m) 121 weeks (f)	51/63 (81%)[b]	8/45 (18%)[b]		
			Day 15	i.p.	75 µg/g body weight	1×	93 weeks (m) 116 weeks (f)	36/60 (60%)[b]	4/55 (7%)[b]		
					150 µg/g body weight	1×	81 weeks (m) 90 weeks (f)	32/55 (58%)[b]	4/55 (7%)[b]		
			Day 42	i.p.	75 µg/g body weight	1×	108 weeks(m)	7/55 (13%)[b]	0/47 (0%)[b]		
					150 µg/g body weight	1×	87 weeks (m)	4/47 (9%)[b]	0/46 (0%)[b]		
	Mice ($C3AF_1$)	liver	Control	Control	None	N/A	142 weeks	8/100 (8%)	1/100 (1%)	+ higher for males. "Age at death" is the average age at which tumors were observed.	
			Day 1	i.p.	75 µg/g body weight	1×	80 weeks (m) 91 weeks (f)	21/62 (34%)[b]	1/45 (2%)[b]		
					150 µg/g body weight	1×	69 weeks (m) 701 weeks (f)	24/52 (46%)[b]	1/56 (2%)[b]		
			Day 15	i.p.	75 µg/g body weight	1×	90 weeks (m) 102 weeks (f)	15/56 (27%)[b]	1/49 (2%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
BaP Benzo[*a*]pyrene (continued)					150 µg/g body weight	1×	77 weeks (m) 62 weeks (f)	12/53 (23%)[b]	1/57 (2%)[b]		
			Day 42	i.p.	75 µg/g body weight	1×		0/30 (0%)[b]	0/32 (0%)[b]		
					150 µg/g body weight	1×	79 weeks (m)	1/32 (3%)[c]	0/40 (0%)[b]		
	Mice ($B6C3F_1$)	lung	Control	Control	Control	N/A	142 weeks	13/100 (13%)	9/100 (9%)	Both sexes developed lung tumors with higher incidence when treated with BaP at birth than at 15 or 42 days of age ($p<0.05$).	
			Day 1	i.p.	75 µg/g body weight	1×	103 weeks (m) 126 weeks (f)	20/47 (43%)[b]	22/45 (49%)[b]		
					150 µg/g body weight	1×	84 weeks (m) 112 weeks (f)	37/63 (59%)[b]	28/45 (62%)[b]		
			Day 15	i.p.	75 µg/g body weight	1×	103 weeks (m) 122 weeks (f)	15/60 (25%)[b]	18/55 (33%)[b]		
					150 µg/g body weight	1×	82 weeks (m) 101 weeks (f)	20/55 (36%)[b]	18/45 (40%)[b]		
			Day 42	i.p.	75 µg/g body weight	1×	119 weeks (m) 131 weeks (f)	20/55 (36%)[b]	12/47 (26%)[b]		
					150 µg/g body weight	1×	95 weeks (m) 118 weeks (f)	18/47 (38%)[b]	8/46 (17%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
BaP Benzo[*a*]pyrene (continued)	Mice ($C3AF_1$)	lung	Control	Control	None	N/A	142 weeks	60/100 (60%)	50/100 (50%)	Of the two mouse strains tested, $C3AF_1$ mice developed significantly more tumors than did the $B6C3F_1$ mice ($p<0.001$).	Vesselinovitch et al. (1975a)
			Day 1	i.p.	75 μg/g body weight	1×	78 weeks (m) 82 weeks (f)	58/62 (93%)[b]	42/45 (93%)[b]		
					150 μg/g body weight	1×	70 weeks (m) 73 weeks (f)	48/52 (92%)[b]	52/56 (93%)[b]		
			Day 15	i.p.	75 μg/g body weight	1×	87 weeks (m) 98 weeks (f)	52/56 (93%)[b]	46/49 (94%)[b]		
					150 μg/g body weight	1×	75 weeks (m) 79 weeks (f)	50/53 (94%)[b]	52/57 (91%)[b]		
			Day 42	i.p.	75 μg/g body weight	1×	91 weeks (m) 93 weeks (f)	28/30 (93%)[b]	28/32 (87%)[b]		
					150 μg/g body weight	1×	85 weeks (m) 83 weeks (f)	28/32 (87%)[b]	36/40 (90%)[b]		
DBA Dibenzanthracene	Mice (Caracul × P stock)	lung	Control	Control	None	N/A	228 days	1/31 (3.2%)			Law (1940)
			Day 1	i.p.	4 mg per cm^3 vehicle	1×	181 days	24/24 (100%)[b]			
			2 months	s.c.	4 mg per cm^3 vehicle	1×	189 days	2/29 (6.9%)[b]			

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
DEN Diethylnitrosamine	Mice ($B6C3F_1$)	liver	Control	Control	Vehicle (0.01 mL trioctanoin/g body weight)	4×	142 weeks (m) 137 weeks (f)	7/98 (7%)	1/100 (1%)	Animals treated as newborns and infants developed significantly more liver tumors than animals that were treated as young adults. Newborns and infant females developed liver tumors at a later age than similarly treated males. Incidences for malignant tumors only.	Vesselinovitch et al. (1984)
			Day 1	i.p. (3-, 6- and 6-day intervals)	1.5 µg/g body weight	4×	67 weeks (m) 90 weeks (f)	37/51 (73%)[b]	45/64 (70%)[b]		
					3 µg/g body weight	4×	65 weeks (m) 80 weeks (f)	40/58 (69%)[b]	44/65 (68%)[b]		
			Day 15		1.5 µg/g body weight	4×	86 weeks (m) 117 weeks (f)	41/57 (72%)[b]	40/71 (56%)[b]		
					3 µg/g body weight	4×	76 weeks (m) 96 weeks (f)	48/69 (70%)[b]	46/62 (74%)[b]		
			Day 42		1.5 µg/g body weight	4×	117 weeks (m) 135 weeks (f)	9/49 (18%)[b]	1/47 (2%)[b]		
					3 µg/g body weight	4×	123 weeks (m) 133 weeks (f)	6/38 (16%)[b]	4/57 (7%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DEN Diethylnitrosamine (continued)	Mice ($C3AF_1$)	liver	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4×	123 weeks (m) 131weeks (f)	8/99 (8%)	1/97 (1%)	Highest tumor rate when dosed at early ages. Newborns and infant females developed liver tumors at a lower incidence than similarly treated males. + higher for males.	Vesselinovitch et al. (1984)
			Day 1	i.p. (3-, 6- and 6-day intervals)	1.5 µg/g body weight	4×	64 weeks (m) 84 weeks (f)	23/32 (72%)[b]	11/39 (28%)[b]		
					3 µg/g body weight	4×	59 weeks (m) 76 weeks (f)	39/58 (67%)[b]	26/50 (52%)[b]		
			Day 15		1.5 µg/g body weight	4×	82 weeks (m) 102 weeks (f)	22/46 (48%)[b]	8/65 (12%)[b]		
					3 µg/g body weight	4×	74 weeks (m) 94 weeks (f)	35/54 (65%)[b]	22/62 (35%)[b]		
			Day 42		1.5 µg/g body weight	4×	105 weeks (m) 106 weeks (f)	12/56 (22%)[b]	0/53 (0%)[b]		
					3 µg/g body weight	4×	105 weeks (m) 103 weeks (f)	9/57 (16%)[b]	0/56 (0%)[b]		
	Mice ($B6C3F_1$)	lung	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4×	142 weeks (m) 137 weeks (f)	13/98 (13%)	9/100 (9%)	The mice treated as newborns showed lung tumors earlier than animals exposed at other times. It is not known whether this was due to actual earlier emergence of tumors or	

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DEN Diethylnitrosamine (continued)			Day 1	i.p. (3-, 6- and 6-day intervals)	1.5 µg/g body weight	4×	70 weeks (m) 91 weeks (f)	29/51 (57%)[b]	49/64 (77%)[b]	to their earlier detection caused by shorter survival.	
					3 µg/g body weight	4×	68 weeks (m) 81 weeks (f)	34/58 (59%)[b]	42/65 (65%)[b]		
			Day 15		1.5 µg/g body weight	4×	87 weeks (m) 115 weeks (f)	51/57 (89%)[b]	61/71 (86%)[b]		
					3 µg/g body weight	4×	77 weeks (m) 97 weeks (f)	51/69 (74%)[b]	53/62 (85%)[b]		
			Day 42		1.5 µg/g body weight	4×	123 weeks (m) 129 weeks (f)	38/49 (78%)[b]	38/47 (81%)[b]		
					3 µg/g body weight	4×	121 weeks (m) 127 weeks (f)	33/38 (87%)[b]	43/57 (75%)[b]		
	Mice ($C3AF_1$)	lung	Control	Control	Vehicle (0.1 trioctanoin/g body weight)	4×	142 weeks (m) 137weeks (f)	60/99 (61%)	50/97 (52%)	Of the two strains, $C3AF_1$ mice developed lung tumors with a higher incidence and multiplicity than $B6C3F_1$ hybrids.	
			Day 1	i.p. (3-, 6- and 6-day intervals)	1.5 µg/g body weight	4×	65 weeks (m) 84 weeks (f)	30/32 (94%)[b]	38/39 (97%)[b]		
					3 µg/g body weight	4×	59 weeks (m) 76 weeks (f)	49/58 (84%)[b]	46/50 (92%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DEN Diethylnitrosamine (continued)			Day 15		1.5 µg/g body weight	4×	80 weeks (m) 101 weeks (f)	42/46 (91%)[b]	61/65 (94%)[b]		
					3 µg/g body weight	4×	74 weeks (m) 92 weeks (f)	50/54 (93%)[b]	57/62 (92%)[b]		
			Day 42		1.5 µg/g body weight	4×	104 weeks (m) 110 weeks (f)	55/56 (98%)[b]	52/53 (98%)[b]		
					3 µg/g body weight	4×	101 weeks (m) 102 weeks (f)	56/57 (98%)[b]	54/56 (96%)[b]		
	Mice ($B6C3F_1$)	liver	Control	Control	None	N/A	90 weeks	1/98 (1%)	0/96 (0%)	Infant animals of both sexes (Day 15) were more sensitive than similarly exposed adults.	Vesselinovitch and Mihailovich (1983)
			Gestation day 18	i.p.	1.5 µg/g body weight	1×		2/50 (4%)[b]	1/51 (2%)[b]		
			Day 15	i.p. (3-, 6- and 6-day intervals)	1.5 µg/g body weight	4×		47/51 (92%)[b]	60/64 (94%)[b]		
			Day 42		1.5 µg/g body weight	4×		13/49 (26%)[b]	3/47 (6%)[b]		
			Day 1	i.p.	1.5 µg/g body weight	1×	73 weeks	15/59 (25%)[b]	—	At the 1.5-µg dose level, 1-day-old mice developed significantly fewer liver tumors than similarly treated infants (Day 15) (p<0.025). Tumor incidence in treated groups versus controls was not evaluated.	Vesselinovitch et al. (1979a)
					5 µg/g body weight	1×		29/45 (64%)[b]	—		
					10 µg/g body weight	1×		24/25 (96%)[b]	—		
			Day 15	i.p.	1.5 µg/g body weight	1×		13/24 (54%)[b]	—		
					5 µg/g body weight	1×		40/54 (74%)[b]	—		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DEN Diethylnitrosamine (continued)					10 µg/g body weight	1×		25/25 (100%)[b]	—		
DMBA Dimethyl-benz[*a*]anthracene	Rats (Sprague-Dawley)	mammary adeno-sarcoma	Day 20	Gavage	10 mg/100 g body weight	1×	Week 25	—	3/6 (50%)[b]	36 of 42 (86%) animals dosed at age 20 days died soon after. Highest number of tumors per animal was in the 46-day group, with decreasing numbers in the older animals. Animals were sacrificed 22 weeks after treatment.	Russo et al. (1979)
			Day 30		10 mg/100 g body weight	1×	Week 26	—	14/15 (93%)[b]		
			Day 40		10 mg/100 g body weight	1×	Week 27	—	8/9 (89%)[b]		
			Day 46		10 mg/100 g body weight	1×	Week 28	—	8/8 (100%)[b]		
			Day 55		10 mg/100 g body weight	1×	Week 29	—	33/34 (97%)[b]		
			Day 70		10 mg/100 g body weight	1×	Week 32	—	5/8 (63%)[b]		
			Day 140		10 mg/100 g body weight	1×	Week 42	—	10/15 (67%)[b]		
			Day 180		10 mg/100 g body weight	1×	Week 47	—	14/26 (54%)[b]		
	Rats (Wistar)	mammary carcinoma[d]	Control 5–8 weeks	Control	None	N/A	17 months	0/22 (0%)	0/25 (0%)	Highest tumor rate in females exposed at 5–8 weeks. Animals were observed for 16 months following treatment.	Meranze et al. (1969)
			Control 26 weeks	Control	None	N/A	20 months	0/31 (0%)	2/20 (10%)		
			< Week 2	Gavage	0.5–1.0 mg	1×	Week 40–56	0/23 (0%)[b]	4/50 (8%)[b]		
			Week 5–8		15 mg	1×	Week 14–55	0/23 (0%)[b]	14/25 (56%)[b]		
			Week 26		15 mg	1×	Week 32–73	0/34 (0%)[b]	4/26 (15%)[b]		
	Rats (Wistar, castrated)	mammary carcinoma	Week 5–8	Gavage	15 mg	1×	Week 14–55	0/21 (0%)[b]	0/22 (0%)[b]		
			Week 26		15 mg	1×	Week 32–73	0/33 (0%)[b]	0/26 (0%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DMBA Dimethyl-benz[*a*]anthracene (continued)	Rats (Wistar)	Total tumors	Control 5–8 weeks	Control	None	N/A	17 months	0/22 (0%)	0/25 (0%)	Total tumors includes leukemia.	
			Control 26 weeks	Control	None	N/A	20 months	2/31 (6%)	5/20 (25%)		
			< Week 2	Gavage	0.5–1.0 mg	1×	Week 40–56	16/23 (70%)[b]	36/50 (72%)[b]		
			Week 5–8		15 mg	1×	Week 14–55	7/23 (30%)[b]	16/25 (64%)[b]		
			Week 26		15 mg	1×	Week 32–73	12/34 (35%)[b]	13/26 (50%)[b]		
	Mice (BALB/c)	lung	Control: Day 1	Control s.c.	Aqueous gelatine	1×	40 weeks	0/12 (0%)	7/23 (30%)	15 µg DMBA gave rise to a significantly greater incidence of lung tumors when administered to newborn mice than to suckling or young adults.	Walters (1966)
			Day 1	s.c.	15 µg	1×	40 weeks[f]	14/14 (100%)[b]	24/24 (100%)[b]		
			Week 2–3 (suckling)	s.c.	15 µg	1×	42–43 weeks	12/23 (52%)[b]	16/22 (73%)[b]		
				s.c.	30 µg (60 µg total)	2×	42–43 weeks	14/14 (100%)[b]	24/24 (100%)[b]		
			Adult[e]	s.c.	15 µg	1×	48-49 weeks	6/12 (50%)[b]	15/33 (45%)[b]		
				s.c.	30 µg (60 µg total)	2×	48-49 weeks	9/10 (90%)[b]	21/23 (91%)[b]		
				s.c.	30 µg (180 µg total)	6×	48-49 weeks	12/12 (100%)[b]	13/13 (100%)[b]		
	Mice (Swiss)	lymphoma	Control	Control	None	N/A	31–52 weeks	3/408 (0.7%)		Higher tumor rates at younger age of exposure. Only one treatment group was exposed i.p.; others were exposed by s.c. injection..	Pietra et al. (1961)
			Day 1	i.p.	30–40 µg	1×	13–33 weeks	6/31 (19%)[b]			
			Day 1	s.c.	30–40 µg	1×	12–27 weeks	8/27 (30%)[b]			
			Week 8	s.c.	900 µg	1×	30 weeks	1/13 (8%)[b]			

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
DMBA Dimethyl-benz[*a*]anthracene (continued)	Mice (Swiss)	lung	Control	Control	None	N/A	31–52 weeks	4/408 (0.9%)			
			Day 1	i.p.	30–40 µg	1×	13–33 weeks	24/31 (77%)[b]			
			Day 1	s.c.	30–40 µg	1×	12–27 weeks	23/27 (85%)[b]			
			Week 8	s.c.	900 µg	1×	30 weeks	2/13 (15%)[b]			
DMN Dimethyl-nitrosamine	Rats (Wistar)	kidney carcinoma	Day 1	i.p.	20 mg/kg	1×	≥5 months	1/33 (3)[b]		In the neonatal group, the dose was reduced to 20 mg/kg to achieve approximately equivalent numbers of survivors. No control group.	Hard (1979)
			Day 21		30 mg/kg	1×		5/39 (13)[b]			
			Month 1		30 mg/kg	1×		2/33 (6)[b]			
			Month 1.5		30 mg/kg	1×		1/28 (4)[b]			
			Month 2		30 mg/kg	1×		1/26 (4)[b]			
			Month 3		30 mg/kg	1×		10/27 (37)[b]			
			Month 4		30 mg/kg	1×		7/32 (22)[b]			
			Month 5		30 mg/kg	1×		0/14 (0)[b]			
	Rats (Wistar)	kidney adenoma	Day 1	i.p.	20 mg/kg	1×	≥5 months	1/33 (3)[b]			
			Day 21		30 mg/kg	1×		13/39 (33)[b]			
			Month 1		30 mg/kg	1×		11/33 (33)[b]			
			Month 1.5		30 mg/kg	1×		13/28 (48)[b]			
			Month 2		30 mg/kg	1×		11/26 (42)[b]			
			Month 3		30 mg/kg	1×		18/27 (67)[b]			
			Month 4		30 mg/kg	1×		17/32 (53)[b]			
			Month 5		30 mg/kg	1×		6/14 (43)[b]			

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
DMN Dimethyl-nitrosamine (continued)	Rats (Wistar)	kidney mesenchymal tumors	Day 1	i.p.	20 mg/kg	1×	≥5 months	8/33 (24)[b]		Mesenchymal tumors were most frequent in the three youngest age groups (z test, $p < 0.001$).	
			Day 21		30 mg/kg	1×		18/39 (46)[b]			
			Month 1		30 mg/kg	1×		23/33 (70)[b]			
			Month 1.5		30 mg/kg	1×		5/28 (19)[b]			
			Month 2		30 mg/kg	1×		2/26 (8)[b]			
			Month 3		30 mg/kg	1×		3/27 (11)[b]			
			Month 4		30 mg/kg	1×		7/32 (22)[b]			
			Month 5		30 mg/kg	1×		0/14 (0)[b]			
	Rats (Wistar)	kidney cortical epithelial tumors	Day 1	i.p.	20 mg/kg	1×	≥5 months	2/33 (6)[b]			Hard (1979)
			Day 21		30 mg/kg	1×		16/39 (41)[b]			
			Month 1		30 mg/kg	1×		12/33 (36)[b]			
			Month 1.5		30 mg/kg	1×		14/28 (52)[b]			
			Month 2		30 mg/kg	1×		11/26 (42)[b]			
			Month 3		30 mg/kg	1×		18/27 (67)[b]			
			Month 4		30 mg/kg	1×		21/32 (66)[b]			
			Month 5		30 mg/kg	1×		6/14 (43)[b]			
	Rats (Wistar)	Total tumors	Day 1	i.p.	20 mg/kg	1×	≥5 months	11/33 (33)[b]			
			Day 21		30 mg/kg	1×		25/39 (64)[b]			
			Month 1		30 mg/kg	1×		25/33 (76)[b]			
			Month 1.5		30 mg/kg	1×		17/28 (63)[b]			
			Month 2		30 mg/kg	1×		13/26 (50)[b]			
			Month 3		30 mg/kg	1×		18/27 (67)[b]			
			Month 4		30 mg/kg	1×		22/32 (69)[b]			
			Month 5		30 mg/kg	1×		7/14 (50)[b]			

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
ENU Ethylnitrosourea	Rats	nervous system	Day 1	Injection	20 mg/kg	1×		100%[b]		Susceptibility to neuro-oncogenic effect declined with increasing age.	Maekawa and Mitsumori (1990)
			Day 30	Injection	20 mg/kg	1×		61%[b]			
	Mice ($B6C3F_1$)	liver	Control	Control	None	N/A	90 weeks	1/98 (1%)	0/96 (0%)	Both male and female mice were responsive to exposure during prenatal and infant life.	Vesselinovitch (1983)
			Gestation day 18	i.p.	60 µg/g body weight	1×		28/52 (54%)[b]	18/49 (37%)[b]		
			Day 15		60 µg/g body weight	1×		41/50 (82%)[b]	28/51 (55%)[b]		
			Day 42		60 µg/g body weight	1×		10/50 (20%)[b]	5/50 (10%)[b]		
	Rats (Wistar)	nerve tissue	Control	Control	None	N/A	4–7 months	0/16 (0%)	0/10 (0%)	Highest tumor rate seen when exposed during gestation or soon after birth. Statistically significant decrease in tumor incidence with increasing age of exposure.	Naito et al. (1981)
			Gestation day 16	i.p.	40 mg/kg	1×		26/26 (100%)[b]	18/18 (100%)[b]		
			Day 1	s.c.	40 mg/kg	1×		12/12 (100%)[g]	16/16 (100%)[g]		
			Week 1		40 mg/kg	1×		12/17 (71%)[b]	18/20 (90%)[b]		
			Week 2		40 mg/kg	1×		10/14 (71%)[b]	14/18 (78%)[b]		
			Week 3		40 mg/kg	1×		6/13 (46%)[b]	5/17 (29%)[b]		
			Week 4		40 mg/kg	1×		8/15 (53%)[b]	2/10 (20%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
ENU Ethylnitrosourea (continued)	Mice ($B6C3F_1$)	lung	Day 1	i.p.	60 µg/g body weight	1×		49/55 (89%)[b]	49/50 (98%)[b]		Vesselinovitch et al. (1974)
			Day 15			1×		50/55 (91%)[b]	47/55 (85%)[b]		
			Day 42			1×		53/59 (90%)[b]	44/51 (86%)[b]		
			Day 1		120 µg/g body weight	1×		36/38 (95%)[b]	54/60 (90%)[b]		
			Day 15			1×		45/49 (92%)[b]	43/50 (86%)[b]		
			Day 42			1×		52/54 (96%)[b]	50/57 (88%)[b]		
	Mice ($C3AF_1$)	lung	Day 1		60 µg/g body weight	1×		46/47 (98%)[g]	51/51 (100%)[g]		
			Day 15			1×		49/49 (100%)[g]	57/59 (97%)[g]		
			Day 42			1×		59/59 (100%)[g]	57/57 (100%)[g]		
			Day 1		120 µg/g body weight	1×		63/64 (98%)[g]	53/57 (93%)[g]		
			Day 15			1×		54/56 (96%)[g]	50/56 (89%)[g]		
			Day 42			1×		59/59 (100%)[g]	48/48 (100%)[g]		
	Mice ($B6C3F_1$)	liver	Day 1	i.p.	60 µg/g body weight	1×		50/54 (93%)[g]	28/43 (65%)[g]		
			Day 15			1×		55/56 (98%)[g]	33/54 (61%)[g]		
			Day 42			1×		12/40 (30%)[b]	6/39 (15%)[b]		
			Day 1		120 µg/g body weight	1×		29/34 (85%)[g]	32/53 (60%)[g]		
			Day 15			1×		45/48 (94%)[g]	29/43 (67%)[g]		
			Day 42			1×		17/49 (35%)[g]	4/50 (8%)[g]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
ENU Ethylnitrosourea (continued)	Mice ($C3AF_1$)	liver	Day 1	i.p.	60 µg/g body weight	1×		42/45 (93%)[g]	19/41 (46%)[g]		
			Day 15			1×		42/50 (84%)[g]	19/48 (40%)[g]		
			Day 42			1×		7/29 (24%)[b]	4/50 (8%)[b]		
			Day 1		120 µg/g body weight	1×		55/62 (89%)[g]	19/45 (42%)[g]		
			Day 15			1×		35/45 (78%)[g]	15/35 (43%)[g]		
			Day 42			1×		8/33 (24%)[b]	3/33 (9%)[b]		
	Mice ($B6C3F_1$)	kidney	Day 1	i.p.	60 µg/g body weight	1×		11/48 (23%)[b]	5/49 (10%)[b]		
			Day 15			1×		6/41 (15%)[b]	7/31 (23%)[b]		
			Day 42			1×		4/40 (10%)[b]	3/37 (8%)[b]		
			Day 1		120 µg/g body weight	1×		10/30 (33%)[g]	14/53 (26%)[b]		
			Day 15			1×		17/37 (46%)[g]	19/49 (39%)[b]		
			Day 42			1×		8/40 (20%)[b]	11/39 (28%)[b]		
	Mice ($C3AF_1$)	kidney	Day 1	i.p.	60 µg/g body weight	1×		7/44 (16%)[b]	6/45 (13%)[b]		
			Day 15			1×		7/41 (17%)[b]	8/46 (17%)[b]		
			Day 42			1×		3/42 (42%)[b]	3/43 (7%)[b]		
			Day 1		120 µg/g body weight	1×		4/52 (7%)[b]	6/29 (21%)[g]		
			Day 15			1×		8/35 (23%)[b]	12/29 (41%)[g]		
			Day 42			1×		6/41 (71%)[b]	3/39 (8%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
ENU Ethylnitrosourea (continued)	Mice (B6C3F1)	Harderian	Day 1		60 µg/g body weight	1×		7/40 (17%)[b]	5/43 (12%)[b]		
			Day 15			1×		10/51 (20%)[b]	17/59 (29%)[b]		
			Day 42			1×		14/50 (28%)[b]	14/45 (31%)[b]		
			Day 1		120 µg/g body weight	1×		9/30 (30%)[g]	6/52 (12%)[b]		
			Day 15			1×		15/41 (37%)[g]	8/31 (26%)[b]		
			Day 42			1×		25/48 (52%)[g]	14/49 (29%)[b]		
	Mice (C3AF$_1$)	Harderian	Day 1		60 µg/g body weight	1×		3/25 (12%)[b]	4/35 (11%)[b]		
			Day 15			1×		1/9 (11%)[b]	6/38 (16%)[b]		
			Day 42			1×		12/48 (25%)[b]	5/33 (15%)[b]		
			Day 1		120 µg/g body weight	1×		3/52 (6%)[b]	1/25 (4%)[b]		
			Day 15			1×		6/46 (13%)[b]	2/52 (4%)[b]		
			Day 42			1×		5/29 (17%)[b]	2/11 (18%)[b]		
	Mice (B6C3F$_1$)	stomach	Day 1		60 µg/g body weight	1×		3/48 (6%)[b]	4/43 (9%)[b]		
			Day 15			1×		10/42 (24%)[g]	7/45 (16%)[b]		
			Day 42			1×		9/51 (18%)[g]	8/36 (22%)[b]		
			Day 1		120 µg/g body weight	1×		2/29 (7%)[b]	9/53 (17%)[b]		
			Day 15			1×		10/35 (29%)[g]	12/33 (36%)[b]		
			Day 42			1×		12/53 (23%)[g]	12/50 (24%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
ENU Ethylnitrosourea (continued)	Mice ($C3AF_1$)	stomach	Day 1		60 µg/g body weight	1×		2/39 (5%)[b]	7/45 (16%)[b]		
			Day 15			1×		7/45 (16%)[g]	7/38 (18%)[b]		
			Day 42			1×		14/55 (25%)[g]	7/49 (14%)[b]		
			Day 1		120 µg/g body weight	1×		8/60 (13%)[b]	9/44 (20%)[b]		
			Day 15			1×		16/51 (31%)[g]	11/42 (26%)[b]		
			Day 42			1×		19/48 (40%)[g]	13/37 (35%)[b]		
	Mice ($B6C3F_1$)	malignant lymphomas	Day 1		60 µg/g body weight	1×		2/55 (4%)[b]	6/52 (12%)[g]		
			Day 15			1×		3/56 (5%)[b]	14/59 (24%)[g]		
			Day 42			1×		9/59 (15%)[b]	17/59 (29%)[g]		
			Day 1		120 µg/g body weight	1×		8/39 (20%)[b]	15/65 (23%)[g]		
			Day 15			1×		14/60 (23%)[b]	17/58 (29%)[g]		
			Day 42			1×		12/59 (20%)[b]	14/60 (23%)[g]		
	Mice ($C3AF_1$)	malignant lymphomas	Day 1		60 µg/g body weight	1×		6/49 (12%)[b]	8/49 (16%)[g]		
			Day 15			1×		3/49 (6%)[b]	13/61 (21%)[g]		
			Day 42			1×		6/60 (10%)[b]	9/55 (16%)[g]		
			Day 1		120 µg/g body weight	1×		3/66 (5%)[b]	10/58 (17%)[g]		
			Day 15			1×		10/56 (18%)[b]	18/60 (30%)[g]		
			Day 42			1×		3/49 (6%)[b]	13/50 (26%)[g]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumor incidence[a]		Comments	Reference
								M	F		
NMU Methylnitrosourea	Mice ($BC3F_1$)	Total tumors	Control	Control	N/A	N/A	60 weeks	1/20 (5%)	0%	Control mice did not exhibit tumors in target sites except a single hepatoma in a male control mouse.	Terracini and Testa (1970)
		lung	Day 1	i.p.	50 µg/g body weight	1×	60 weeks	12/15 (80%)[b]	16/19 (84%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	10/26 (39%)[b]	10/35 (29%)[b]		
		lympho-sarcoma	Day 1		50 µg/g body weight	1×	60 weeks	23/39 (59%)[b]	23/45 (51%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	11/35 (31%)[b]	21/45 (47%)[b]		
		liver	Day 1		50 µg/g body weight	1×	60 weeks	10/12 (83%)[b]	1/17 (6%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	0%[b]	0%[c]		
		kidney	Day 1		50 µg/g body weight	1×	60 weeks	3/15 (20%)[b]	3/18 (17%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	2/21 (10%)[b]	0%[c]		
		fore-stomach	Day 1		50 µg/g body weight	1×	60 weeks	0%[b]	4/17 (24%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	8/22 (36%)[b]	12/18 (67%)[b]		
	Rats (Wistar)	mammary	Day 1	i.p.	50 µg/g body weight	1×	60 weeks	0%[b]	4/14 (29%)[b]	Tumor incidence for control rats was based on previous experiments (Della Porta et al., 1968) and was not specifically reported in this paper.	Terracini and Testa (1970)
			5 weeks		50 µg/g body weight	1×	60 weeks	0%[b]	3/5 (60%)[b]		
		lympho-sarcoma	Day 1		50 µg/g body weight	1×	60 weeks	1/10 (10%)[b]	0%[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	2/8 (25%)[b]	1/11 (9%)[b]		
		kidney (ana-plastic)	Day 1		50 µg/g body weight	1×	60 weeks	14/18 (78%)[b]	9/13 (69%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	2/5 (40%)[b]	5/12 (42%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumor incidence[a] M	Tumor incidence[a] F	Comments	Reference
NMU Methylnitrosourea (continued)		kidney (adenoma)	Day 1		50 µg/g body weight	1×	60 weeks	3/14 (21%)[b]	2/6 (33%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	¼ (25%)[b]	0%[b]		
		forestomach	Day 1		50 µg/g body weight	1×	60 weeks	4/14 (29%)[b]	3/6 (50%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	0%[c]	0%[b]		
		intestine	Day 1		50 µg/g body weight	1×	60 weeks	3/10 (30%)[b]	2/2 (100%)[b]		
			5 weeks		50 µg/g body weight	1×	60 weeks	2/4 (50%)[b]	0%[b]		
	Mice (C3Hf/Dp)	thymus	control	i.p.	NA	NA	120 wks[**]	0/34 (0%)	0/25 (0%)	[*]Age at death from thymic lymphoma reported specifically for some, but not all, dose groups. [**]Control mice were sacrificed at 120 wks. [***]Age of death for all mice in this dose group, regardless of cancer type.	Terracini et al. (1976)
			Day 1		25 µg NMU/g body weight	1×	29 ± 8.4 wks	2/16 (13%)[b]	5/25 (20%)[b]		
			Day 70		25 µg NMU/g body weight	1×	120 wks (M)[***] 100 wks (F)	0/20 (0%)[c]	1/20 (5%)[b]		
			Day 1		50 µg NMU/g body weight	1×	16.5 ± 0.7 wks	16/24 (67%)[b]	30/44 (68%)[b]		
			Day 21		50 µg NMU/g body weight	1×	24.5 ± 2.5 wks	14/44 (32%)[b]	18/38 (47%)[b]		
			Day 70		50 µg NMU/g body weight	1×	31.4 ± 4.4 wks	9/30 (30%)[b]	6/41 (15%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death		Tumor incidence		Reference
							M	F	M	F	
NMU Methylnitrosourea (continued)	Mice (C3Hf/Dp)	extra-thymic lymphoma	control	i.p.	NA	NA	120 weeks	120 weeks	1/34 (3%)	2/25 (8%)	Terracini et al. (1976)
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	2/16 (13%)[b]	1/25 (4%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	0/20 (0%)[b]	0/20 (0%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	0/24 (0%)[b]	0/44 (0%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	1/44 (2%)[b]	0/38 (0%)[b]	
			Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	1/30 (3%)[b]	0/41 (0%)[b]	
		lung	control	i.p.	NA	NA	120 weeks	120 weeks	4/34 (12%)	6/25 (24%)	
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	7/16 (44%)[b]	13/25 (52%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	12/20 (60%)[b]	8/20 (40%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	5/24 (21%)[b]	11/44 (25%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	23/44 (52%)[b]	15/38 (39%)[b]	
			Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	18/30 (60%)[b]	24/41 (59%)[b]	
		liver	control	i.p.	NA	NA	120 weeks	120 weeks	13/34 (38%)	1/25 (4%)	Terracini et al. (1976)
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	9/16 (56%)[g]	2/25 (8%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	12/20 (60%)[g]	2/20 (10%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	4/24 (17%)[g]	3/44 (7%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	21/44 (48%)[g]	1/38 (2.6%)[b]	

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death M	Age at death F	Tumor incidence M	Tumor incidence F	Reference
NMU Methylnitrosourea (continued)	Mice (C3Hf/Dp)		Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	8/30 (27%)[g]	2/41 (5%)[b]	
		stomach	control	i.p.	NA	NA	120 weeks	120 weeks	0/34 (0%)	5/25 (20%)	
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	2/16 (13%)[b]	10/25 (40%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	3/20 (15%)[b]	7/20 (35%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	2/24 (8%)[b]	1/44 (2%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	19/44 (43%)[b]	9/38 (24%)[b]	
			Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	8/30 (27%)[b]	21/41 (51%)[b]	
		kidney	control	i.p.	NA	NA	120 weeks	120 weeks	0/34 (0%)	0/25 (0%)	Terracini et al. (1976)
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	0/16 (0%)[b]	0/25 (0%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	0/20 (0%)[b]	0/20 (0%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	0/24 (0%)[b]	4/44 (9%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	1/44 (2%)[b]	4/38 (11%)[b]	
			Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	5/30 (17%)[b]	7/41 (17%)[b]	

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death		Tumor incidence		Reference
							M	F	M	F	
NMU Methylnitrosourea (continued)	Mice (C3Hf/Dp)	ovary	control	i.p.	NA	NA	120 weeks	120 weeks	NA	3/25 (12%)	
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	NA	2/25 (8%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	NA	4/20 (20%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	NA	0/44 (0%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	NA	9/38 (24%)[b]	
			Day 70		50 µg NMU/g body weight	1×	110 weeks	90 weeks	NA	16/41 (39%)[b]	
		mammary	control	i.p.	NA	NA	120 weeks	120 weeks	NA	2/25 (8%)	Terracini et al. (1976)
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	NA	1/25 (4%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	NA	0/20 (0%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	NA	0/44 (0%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	1/44 (2%)[b]	0/38 (0%)[b]	
			Day 70		50 µg NMU/g body weight		110 weeks	90 weeks	NA	4/41 (9.8%)[b]	
		uterus or vagina	control	i.p.	NA	NA	120 weeks	120 weeks	NA	1/25 (4%)	
			Day 1		25 µg NMU/g body weight	1×	100 weeks	90 weeks	NA	1/25 (4%)[b]	
			Day 70		25 µg NMU/g body weight	1×	120 weeks	100 weeks	NA	6/20 (30%)[b]	
			Day 1		50 µg NMU/g body weight	1×	70 weeks	80 weeks	NA	0/44 (0%)[b]	
			Day 21		50 µg NMU/g body weight	1×	100 weeks	90 weeks	NA	1/38 (3%)[b]	
			Day 70		50 µg NMU/g body weight		110 weeks	90 weeks		7/41 (17%)[b]	

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
Urethane	Mice (SWR)	lung adenoma	Newborn	s.c.	0.18 mg/g body weight	1×	10 weeks	100%[b]		The average number of tumors per mouse increased linearly with dose.	Kaye and Trainin (1966)
			11–22 weeks	s.c.	0.25 mg/g body weight	1×	23–34 weeks	0%[b]			
	Mice (C3H/f)	liver	Control	Control	None	N/A	493 days (m) 553 days (f)	14/97 (14%)	1/77 (1%)		Liebelt et al. (1964)
			Day 1	i.p.	0.8 mg/g body weight	1×	481 days (m) 434 days (f)	27/30 (90%)[g]	18/39 (46%)[g]		
			8–10 weeks	i.p.	1 mg/g body weight	1×	321 days (m) -	6/25 (24%)[c]	0/32 (0%)[c]		
		lung	Control	Control	None	N/A	493 days (m) 553 days (f)	0/97 (0%)	0/77 (0%)	The number of lung tumors among the controls was not provided.	
			Day 1	i.p.	0.8 mg/g body weight	1×	401 days (m) 408 days (f)	14/30 (46%)[g]	19/39 (48%)[g]		
			8–10 weeks	i.p.	1 mg/g body weight	1×	506 days (m) -	2/25 (8%)[c]	0/32 (0%)[c]		
		reticular tissue	Control	Control	None	N/A	493 days (m) 553 days (f)	2/97 (2%)	6/77 (8%)		
			Day 1	i.p.	0.8 mg/g body weight	1×	285 days (m) 343 days (f)	4/30 (13%)[c]	22/39 (56%)[g]		
			8–10 weeks	i.p.	1 mg/g body weight	1×	- 453 days (f)	0/25 (25%)[c]	4/32 (13%)[c]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a]		Comments	Reference
								M	F		
Urethane (continued)	Mice (Swiss)	leukemia	Control	Control	None	N/A	8–10 months	1%		Highest tumor rates when dosed at birth.	Fiore-Donati et al. (1962)
			Day 1	s.c.	2 mg in 0.05 mL aqueous solution	1×		13/60 (22%)[b]		Exposure to newborns was followed by 21.6% leukemia, occurring at a mean age of 105 days.	
			Day 5		4 mg in 0.05 mL aqueous solution	1×		7/39 (18%)[b]			
			Day 40		20 mg in 0.1 mL aqueous solution	1×		2/63 (3%)[b]			
	Mice (Swiss)	lung adenoma	Control 2 weeks	Control	None	N/A	9 weeks	0/15 (0%)	—	The proportion of animals with adenomas decreased steadily with age of exposure.	Rogers (1951)
			Control 4 weeks	Control	None	N/A	11 weeks	0/14 (0%)	—		
			Control 6 weeks	Control	None	N/A	13 weeks	1/15 (7%)	—		
			Control 8 weeks	Control	None	N/A	15 weeks	2/15 (13%)	—		
			Control 10 weeks	Control	None	N/A	17 weeks	0/15 (0%)	—		
			2 weeks	i.p.	1 mg/g body weight	1×	9 weeks	24/24 (100%)[b]	—		
			4 weeks	i.p.	1 mg/g body weight	1×	11 weeks	23/25 (92%)[b]	—		
			6 weeks	i.p.	1 mg/g body weight	1×	13 weeks	22/25 (88%)[b]	—		
			8 weeks	i.p.	1 mg/g body weight	1×	15 weeks	21/25 (84%)[b]	—		
			10 weeks	i.p.	1 mg/g body weight	1×	17 weeks	19/25 (76%)[b]	—		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumors[a] M	Tumors[a] F	Comments	Reference
Urethane (continued)	Mice (Swiss)	lung adenoma	3 weeks	i.p.	0.25 mg/g body weight	1×	12 weeks	16/19 (84%)[b]	—		
					0.5 mg/g body weight	1×	12 weeks	16/20 (80%)[b]	—		
					1 mg/g body weight	1×	12 weeks	18/20 (90%)[b]	—		
			8 weeks	i.p.	0.25 mg/g body weight	1×	17 weeks	4/17 (24%)[b]	—		
					0.5 mg/g body weight	1×	17 weeks	15/16 (94%)[b]	—		
					1 mg/g body weight	1×	17 weeks	18/18 (100%)[b]	—		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumor incidence[a]		Comments	Reference
								M	F		
Urethane (continued)	Mice (Swiss)	liver	Control	Control	N/A	N/A	360–720 days	10/227 (4.4%)	4/222 (8.22%)		Chieco-Bianchi et al. (1963)
			Day 1	s.c.	1 mg/g body weight	1×	180 days	1/20 (5%)[g]	0/20 (0%)[c]		
			Day 1	s.c.	1 mg/g body weight	1×	240 days	2/17 (12%)[g]	0/12 (0%)[c]		
			Day 1	s.c.	1 mg/g body weight	1×	300 days	5/18 (28%)[g]	0/16 (0%)[c]		
			Day 1	s.c.	1 mg/g body weight	1×	360 days	11/20 (55%)[g]	0/23 (0%)[c]		
			Day 1	s.c.	1 mg/g body weight	1×	420 days	13/15 (87%)[g]	2/22 (9%)[g]		
			Day 1	s.c.	1 mg/g body weight	1×	480 days	17/23 (74%)[c]	2/25 (8%)[c]		
			Day 5	s.c.	1 mg/g body weight	1×	420 days	9/13 (69.2%)[b]	2/11 (18.2%)[b]		
			Day 20	s.c.	1 mg/g body weight	1×	420 days	1/13 (8%)[b]	0/16 (0%)[b]		
			Day 40	s.c.	1 mg/g body weight	1×	420 days	0/11 (0%)[b]	0/9 (0%)[b]		
	Mice (Swiss)	skin	Control	Control	N/A	N/A	180–550 days	30/712 (4.21%)		Croton oil treatment initiated at 40 days of age.	Chieco-Bianchi et al. (1963)
			Day 1	s.c.	1 mg urethane/g body weight; 5% croton oil	single dose urethane, croton oil applied 2×/week for 10 mos	660 days	26/59 (44.1%)[g]			

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumor incidence[a]		Comments	Reference
								M	F		
Urethane (continued)			Day 40	s.c.	1 mg urethane/g body weight; 5% croton oil	single dose urethane, croton oil applied 2×/week for 10 mos	700 days	8/41 (19.5%)[b]			
	Mice ($B6AF_1/J$)	liver	Control	gavage	N/A	N/A	71 weeks	1/25 (4%)	0/25 (0%)		Klein (1966)
			Day 1		1 mg/g body weight	1×	66 weeks	9/20 (45%)[g]	9/26 (35%)[g]		
			Day 7		1 mg/g body weight	1×	67 weeks	20/22 (91%)[g]	20/26 (77%)[g]		
			Day 14		1 mg/g body weight	1×	68 weeks	16/20 (80%)[g]	10/23 (43%)[g]		
			Day 21		1 mg/g body weight	1×	69 weeks	13/23 (57%)[g]	1/20 (5%)[g]		
			Day 28		1 mg/g body weight	1×	70 weeks	4/24 (17%)[g]	1/20 (5%)[g]		
		lung	Control	gavage	1 mg/g body weight	1×	71 weeks	9/25 (36%)	6/25 (24%)		
			Day 1		1 mg/g body weight	1×	66 weeks	20/20 (100%)[b]	25/26 (96%)[b]		
			Day 7		1 mg/g body weight	1×	67 weeks	22/22 (100%)[b]	26/26 (100%)[b]		
			Day 14		1 mg/g body weight	1×	68 weeks	19/20 (95%)[b]	19/23 (83%)[b]		
			Day 21		1 mg/g body weight	1×	69 weeks	23/23 (100%)[b]	19/20 (95%)[b]		
			Day 28		1 mg/g body weight	1×	70 weeks	24/24 (100%)[b]	20/20 (100%)[b]		
	Mice ($B6AF_1/J$)	Harderian gland	Control	gavage	1 mg/g body weight	1×	71 weeks	0/25 (0%)	0/25 (0%)		Klein (1966)
			Day 1		1 mg/g body weight	1×	66 weeks	0/20 (0%)[c]	1/26 (4%)[b]		

Table 3. Methodological information and tumor incidence for animal studies with early postnatal and juvenile and adult acute exposure (continued)

Chemical	Species (strain)	Target site	Age when first dosed	Dose route, # doses	Dose	Duration of exposure	Age at death	Tumor incidence[a] M	Tumor incidence[a] F	Comments	Reference
Urethane (continued)			Day 7		1 mg/g body weight	1×	67 weeks	0/22 (0%)[c]	1/26 (4%)[b]		
			Day 14		1 mg/g body weight	1×	68 weeks	0/20 (0%)[c]	2/23 (9%)[b]		
			Day 21		1 mg/g body weight	1×	69 weeks	1/23 (4%)[b]	0/20 (0%)[c]		
			Day 28		1 mg/g body weight	1×	70 weeks	0/24 (0%)[c]	0/20 (0%)[c]		
		forestomach	Control	gavage	1 mg/g body weight	1×	71 weeks	0/25 (0%)	1/25 (4%)		
			Day 1		1 mg/g body weight	1×	66 weeks	0/20 (0%)[c]	3/26 (12%)[b]		
			Day 7		1 mg/g body weight	1×	67 weeks	1/22 (5%)[b]	1/26 (4%)[b]		
			Day 14		1 mg/g body weight	1×	68 weeks	1/20 (5%)[b]	4/23 (17%)[b]		
			Day 21		1 mg/g body weight	1×	69 weeks	0/23 (0%)[c]	1/20 (5%)[b]		
			Day 28		1 mg/g body weight	1×	70 weeks	2/24 (8%)[b]	1/20 (5%)[b]		

[a] Where not delineated by gender, data combined by study authors or gender not specified. Where percentages only are given, number of subjects not specified.
[b] Not evaluated by authors.
[c] Evaluated but not significant compared with controls.
[d] Study also included mammary fibroadenomas and fibromas as well as other types of cancers.
[e] 8–9 weeks old.
[f] Includes survivors up to 40 weeks only.
[g] Significant compared with controls.

i.p. = intraperitoneal injection; s.c. = subcutaneous injection

Table 4. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to carcinogens with a mutagenic mode of action*

Compound	Species (strain)	Sex	Dose	Tumor	Unweighted geometric mean	2.5%	Median	97.5%	Reference
Benzidine	Mice ($B6C3F_1$)	male		liver	111	64	**110**	198	Vesselinovitch et al. (1975b)
		female		liver	0.16	0.004	**0.22**	1.1	
3-MU 3-Methylcholanthrene (formerly known as 20-methylcholanthrene)	Mice (Albino)	male	0.25 mg/g	hepatoma	33	7.4	**30**	268	Klein (1959)
		female	0.25 mg/g	hepatoma	7.7	1.1	**7.1**	85	
		male	0.25 mg/g	forestomach	0.91	0.39	**0.91**	2.1	
		female	0.25 mg/g	forestomach	1.5	0.58	**1.5**	4.2	
		male	0.25 mg/g	skin	1.8	0.048	**2.1**	22	
		female	0.25 mg/g	skin	1.5	0.023	**1.8**	21	
Safrole	Mice ($B6C3F_1$)	male		liver	47	16	**44**	198	Vesselinovitch et al. (1979b)
		female		liver	0.12	0.002	**0.18**	1.1	
VC Vinyl chloride	Rats (Sprague-Dawley)	male	6,000 ppm	liver-angiosarcoma	6.7	0.035	**9.8**	57	Maltoni et al. (1984)
		male	10,000 ppm	liver-angiosarcoma	7.4	0.035	**11**	62	
		female	6,000 ppm	liver-angiosarcoma	13	4.9	**13**	33	
		female	10,000 ppm	liver-angiosarcoma	30	8.7	**29**	121	
		male	6,000 ppm	zymbal gland	0.73	0.0032	**1.1**	30	
		male	10,000 ppm	zymbal gland	0.27	0.0022	**0.4**	5.4	
		female	6,000 ppm	zymbal gland	0.48	0.0027	**0.7**	16	
		female	10,000 ppm	zymbal gland	0.15	0.0014	**0.19**	4.5	
		male	10,000 ppm	leukemia	21	0.026	**37**	514	
		female	6,000 ppm	leukemia	1.3	0.0035	**1.7**	153	
		female	10,000 ppm	leukemia	0.29	0.0019	**0.35**	17	
		male	6,000 ppm	nephroblastomas	0.15	0.0014	**0.19**	4.8	
		male	10,000 ppm	nephroblastomas	0.17	0.0015	**0.21**	6.2	
		female	6,000 ppm	nephroblastomas	0.28	0.0018	**0.33**	16	
		female	10,000 ppm	nephroblastomas	0.24	0.0017	**0.29**	11	
		male	6,000 ppm	angiosarcomas-other sites	0.9	0.0033	**1.26**	53	
		male	10,000 ppm	angiosarcomas-	0.25	0.0017	**0.30**	12	

Table 4. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to mutagenic chemicals (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Unweighted geometric mean	2.5%	Median	97.5%	Reference
				other sites					
VC Vinyl chloride (continued)		female	6,000 ppm	angiosarcomas-other sites	0.24	0.0017	**0.29**	11	
		female	10,000 ppm	angiosarcomas-other sites	0.32	0.0019	**0.38**	20	
		male	6,000 ppm	angiomas & fibromas-other sites	0.72	0.0031	**1.0**	33	
		male	10,000 ppm	angiomas & fibromas-other sites	1.4	0.0045	**2.36**	47	
		female	6,000 ppm	angiomas & fibromas-other sites	0.27	0.0018	**0.33**	16	
		female	10,000 ppm	angiomas & fibromas-other sites	0.52	0.0024	**0.63**	41	
		male	6,000 ppm	hepatoma	62	11	**58**	543	
		male	10,000 ppm	hepatoma	34	8.2	**32**	218	
		female	6,000 ppm	hepatoma	55	13	**51**	352	
		female	10,000 ppm	hepatoma	55	8.4	**53**	513	
		male	6,000 ppm	skin carcinomas	1.1	0.0035	**1.5**	82	
		male	10,000 ppm	skin carcinomas	0.41	0.0024	**0.56**	15	
		female	6,000 ppm	skin carcinomas	0.46	0.0024	**0.59**	24	
		female	10,000 ppm	skin carcinomas	0.31	0.0019	**0.37**	19	
		male	6,000 ppm	neuroblastoma	0.21	0.0016	**0.26**	9.5	
		male	10,000 ppm	neuroblastoma	0.20	0.0016	**0.24**	8.5	
		female	6,000 ppm	neuroblastoma	0.27	0.0018	**0.32**	15	
		female	10,000 ppm	neuroblastoma	0.14	0.0014	**0.18**	4.4	

* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

Table 5. Ratio of early-life to adult cancer potencies for studies with repeated exposures of juvenile and adult animals to chemicals with a nonmutagenic mode of action*

Compound	Species (strain)	Sex	Dose	Tumor	Ratio of juvenile to adult potency				Reference
					Unweighted geometric mean	2.5%	Median	97.5%	
Amitrole	Mice ($B6C3F_1$)	male	NA	liver	13	5.1	**14**	30	Vesselinovitch (1983)
		female	NA	liver	0.14	0.0013	**0.18**	3.9	
DDT	Mice ($B6C3F_1$)	male	NA	liver	1.3	0.0044	**2.5**	25	Vesselinovitch et al. (1979a)
Dieldrin	Mice ($B6C3F_1$)	male	NA	liver	0.75	0.0031	**1.2**	27	Vesselinovitch et al. (1979a)
DPH	Rats (F344/N)	male	630	liver	0.4	0.0024	**0.54**	16	Chhabra et al. (1993b)
		female	630	liver	0.24	0.0017	**0.29**	12	
	Mice ($B6C3F_1$)	male	210	liver	1.5	0.0040	**2.4**	71	
		female	210	liver	1.3	0.0056	**2.6**	15	
ETU	Rats (F344/N)	male	90	thyroid	0.37	0.0029	**0.61**	5.4	Chhabra et al. (1992)
		female	90	thyroid	0.23	0.0018	**0.3**	7.0	
	Mice ($B6C3F_1$)	male	330	liver	0.091	0.0011	**0.12**	1.9	
		female	330	liver	0.057	0.0010	**0.081**	0.65	
		male	330	thyroid	0.41	0.0022	**0.52**	25	
		female	330	thyroid	0.4	0.0024	**0.55**	16	
		male	330	pituitary	0.32	0.0019	**0.38**	22	
		female	330	pituitary	0.24	0.0018	**0.32**	6.9	
PBB	Rats (F344/N)	male	10	liver	0.59	0.0041	**1.1**	6.6	Chhabra et al. (1993a)
		female	10	liver	0.063	0.0009	**0.079**	1.2	
		male	10	mononuclear cell leukemia	0.79	0.0035	**1.4**	18	
		female	10	mononuclear cell leukemia	0.21	0.0017	**0.28**	6.0	
	Mice ($B6C3F_1$)	male	30	liver	3.9	1.9	**3.9**	7.5	
		female	30	liver	1.0	0.37	**1.05**	2.1	

* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action*

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
BaP*	Mice (B6C3F$_1$)	male	75 µg/kg	liver	1 day	9.3	2.9	**8.4**	55	Vesselinovitch et al. (1975a)
					15 days	11	3.5	**9.6**	61	
		female	75 µg/kg		1 day	1.2	0.0083	**1.6**	31	
					15 days	1.7	0.015	**2.1**	36	
		male	150 µg/kg		1 day	29	8.2	**26**	194	
					15 days	15	4.1	**13**	109	
		female	150 µg/kg		1 day	8.8	1.4	**8.1**	94	
					15 days	1.2	0.0082	**1.6**	30	
	Mice (C3AF$_1$)	male	75 µg/kg	liver	1 day	11	2.1	**10**	112	
					15 days	7.5	1.1	**7.0**	83	
		female	75 µg/kg		1 day	0.2	0.0018	**0.26**	9.1	
					15 days	0.2	0.0017	**0.24**	8.5	
		male	150 µg/kg		1 day	14	3.0	**12.8**	130	
					15 days	3.6	0.11	**3.8**	49	
		female	150 µg/kg		1 day	0.2	0.0017	**0.24**	8.8	
					15 days	0.2	0.0017	**0.24**	8.7	
	Mice (B6C3F$_1$)	Male	75 µg/kg	lung	1 day	1.2	0.45	**1.2**	3.4	
					15 days	0.2	0.0046	**0.31**	1.4	
		female	75 µg/kg	lung	1 day	2.8	1.096	**2.7**	9.5	
					15 days	1.4	0.41	**1.4**	5.1	
		Male	150 µg/kg	lung	1 day	2.2	1.0	**2.1**	5.4	
					15 days	0.8	0.2	**0.82**	2.3	
		female	150 µg/kg	lung	1 day	7.9	2.6	**7.2**	43	
					15 days	3.7	1.1	**3.4**	22	
	Mice (C3AF$_1$)	male	75 µg/kg	lung	1 day	1.2	0.47	**1.2**	3.2	
					15 days	1.1	0.43	**1.08**	3.1	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
BaP* (continued)		female	75 µg/kg	lung	1 day	1.6	0.66	**1.55**	4.0	
					15 days	1.6	0.71	**1.63**	4.2	
		male	150 µg/kg	lung	1 day	1.5	0.57	**1.5**	5.0	
					15 days	1.9	0.71	**1.8**	6.0	
		female	150 µg/kg	lung	1 day	1.3	0.61	**1.3**	2.9	
					15 days	1.2	0.54	**1.1**	2.6	
DBA	Mice			lung		178	20	**143**	5100	Law (1940)
DEN**	Mice (B6C3F$_1$)	male	6 µg/kg	liver	1 day	9.0	3.5	**8.3**	37	Vesselinovitch et al. (1984)
					15 days	8.9	3.5	**8.2**	36	
		female	6 µg/kg	liver	1 day	35	9.1	**31**	239	
					15 days	25	6.3	**226**	175	
		male	12 µg/kg	liver	1 day	9.6	3.3	**8.8**	50	
					15 days	9.8	3.4	**8.9**	51	
		female	12 µg/kg	liver	1 day	16	5.9	**15**	67	
					15 days	19	7.1	**18**	79	
	Mice (C3AF$_1$)	male	6 µg/kg	liver	1 day	7.3	2.9	**6.9**	26	
					15 days	3.5	1.4	**3.3**	13	
		female	6 µg/kg	liver	1 day	17	3.2	**16**	166	
					15 days	6.4	0.86	**6.0**	73	
		male	12 µg/kg	liver	1 day	11	3.7	**9.5**	53	
					15 days	9.8	3.4	**8.9**	50	
		female	12 µg/kg	liver	1 day	40	8.5	**36**	340	
					15 days	25	5.0	**22**	221	
	Mice (B6C3F$_1$)	male	6 µg/kg	lung	1 day	0.5	0.27	**0.52**	0.93	
					15 days	1.6	0.95	**1.6**	2.7	
		female	6 µg/kg	lung	1 day	0.9	0.54	**0.89**	1.5	
					15 days	1.2	0.76	**1.2**	2.0	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
DEN** (continued)		male	12 µg/kg	lung	1 day	0.4	0.21	**0.40**	0.73	
					15 days	0.7	0.39	**0.66**	1.1	
		female	12 µg/kg	lung	1 day	0.7	0.44	**0.73**	1.2	
					15 days	1.4	0.88	**1.4**	2.3	
	Mice (C3AF$_1$)	male	6 µg/kg	lung	1 day	0.7	0.22	**0.67**	1.7	
					15 days	0.5	0.21	**0.56**	1.3	
		female	6 µg/kg	lung	1 day	1.1	0.45	**1.1**	2.5	
					15 days	0.7	0.36	**0.74**	1.5	
		male	12 µg/kg	lung	1 day	0.3	0.084	**0.33**	0.76	
					15 days	0.6	0.26	**0.62**	1.4	
		female	12 µg/kg	lung	1 day	0.7	0.35	**0.75**	1.6	
					15 days	0.7	0.37	**0.75**	1.5	
DMBA[#]	Rats (Wistar)	male		total	2 vs 5–8 wks	3.3	1.3	**3.2**	10	Meranze et al. (1969)
					2 vs 26 wks	3.2	1.3	**3.1**	9.7	
		female		total	2 vs 5–8 wks	1.3	0.68	**1.3**	2.5	
					2 vs 26 wks	3.3	1.2	**3.0**	16	
				mammary	2 vs 5–8 wks	0.0	0.0012	**0.056**	0.26	
					2 vs 26 wks	0.2	0.0023	**0.29**	5.3	
					5 vs 26 wks	7.1	1.8	**6.4**	55	
	Mice (Balb/c)	male	15 µg	lung	1 day	30	2.8	**22**	1482	Walters (1966)
					15–19 days	1.0	0.28	**1.0**	3.5	
		male	30 µgx2	lung	15–19 days	14	1.056	**10**	978	
		female	15 µg	lung	1 day	60	6.0	**46**	2350	
					15–19 days	3.1	0.51	**3.0**	22	
		female	30 µgx2	lung	15–19 days	15	1.2	**11**	1004	
	Mice (Swiss)			lymphoma		2.7	0.60	**2.5**	19	Pietra et al. (1961)
				lung		9.1	2.9	**8.7**	40	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
DMN***	Rats (Wistar)		3 wks	total	1 month	0.7	0.41	**0.73**	1.3	Hard (1979)
					1.5 months	1.1	0.58	**1.1**	2.1	
					2 months	1.5	0.75	**1.5**	3.0	
					3 months	0.9	0.50	**0.94**	1.8	
			24 hr		1 month	0.3	0.13	**0.28**	0.6	
					1.5 months	0.4	0.18	**0.42**	0.9	
					2 months	0.6	0.24	**0.56**	1.3	
					3 months	0.4	0.16	**0.36**	0.78	
			1 month		1.5 months	1.5	0.80	**1.52**	3.0	
					2 months	2.0	1.0	**2.0**	4.2	
					3 months	1.3	0.69	**1.3**	2.5	
ENU	Mice ($B6C3F_1$)	male		liver		7.8	3.9	**7.7**	18	Vesselinovitch (1983)
		female				7.1	2.9	**6.9**	21	
	Rats (Wistar)	male		nerve tissue	1 day	27	2.5	**20**	1374	Naito et al. (1981)
					1 week	1.6	0.61	**1.6**	4.6	
					2 weeks	1.6	0.58	**1.6**	4.8	
					3 weeks	0.7	0.12	**0.72**	2.3	
		female			1 day	64	6.0	**50**	2488	
					1 weeks	9.6	2.6	**8.9**	59	
					2 weeks	6.2	1.6	**5.7**	40	
					3 weeks	0.7	0.0090	**0.89**	8.9	
	Mice ($B6C3F_1$)	male	60 µg/g	lung	1	1.0	0.60	**1.0**	1.7	Vesselinovitch et al. (1974)
					15	1.1	0.66	**1.1**	1.8	
		female	60 µg/g	lung	1	2.1	1.17	**2.1**	4.1	
					15	1.0	0.60	**1.0**	1.7	
		male	120 µg/g	lung	1	1.0	0.60	**1.0**	1.7	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency: Unweighted geometric mean	2.5%	Median	97.5 %	Reference
					15	1.1	0.66	**1.0**	1.8	
ENU (continued)		female	120 μg/g	lung	1	2.1	1.2	**2.1**	4.1	
					15	1.0	0.60	**1.0**	1.7	
	Mice (C3AF$_1$)	male	60 μg/g	lung	1	8.7	2.7	**8.0**	48	
					15	52	5.2	**39**	2141	
		female	60 μg/g	lung	15	0.7	0.32	**0.72**	1.6	
		male	120 μg/g	lung	1	0.9	0.38	**0.92**	2.2	
					15	0.7	0.28	**0.67**	1.6	
		female	120 μg/g	lung	1	0.5	0.24	**0.54**	1.2	
					15	0.4	0.18	**0.42**	0.92	
	Mice (B6C3F$_1$)	male	60 μg/g	liver	1	8.8	4.2	**8.5**	22	
					15	14	6.2	**14**	37	
		female	60 μg/g	liver	1	6.3	2.6	**6.1**	18	
					15	5.6	2.4	**5.4**	16	
		male	120 μg/g	liver	1	5.2	2.5	**5.1**	11	
					15	7.6	3.9	**7.5**	17	
		female	120 μg/g	liver	1	11	4.1	**11**	46	
					15	14	4.9	**13**	55	
	Mice (C3AF$_1$)	male	60 μg/g	liver	1	12	4.7	**11**	43	
					15	8.1	3.2	**7.6**	29	
		female	60 μg/g	liver	1	7.5	2.6	**7.0**	32	
					15	4.8	1.8	**4.6**	18	
		male	120 μg/g	liver	1	9.8	4.1	**9.3**	32	
					15	6.6	2.7	**6.3**	23	
		female	120 μg/g	liver	1	5.4	1.7	**5.0**	25	
					15	5.4	1.7	**5.1**	25	
	Mice (B6C3F$_1$)	male	60 μg/g	kidney	1	2.2	0.73	**2.1**	8.0	
					15	1.2	0.29	**1.2**	5.1	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency: Unweighted geometric mean	2.5%	Median	97.5 %	Reference
		female	60 µg/g	kidney	1	0.7	0.024	**0.85**	5.9	
					15	2.6	0.61	**2.5**	15	
ENU (continued)		male	120 µg/g	kidney	1	1.7	0.65	**1.7**	4.4	
					15	2.6	1.14	**2.6**	6.4	
		female	120 µg/g	kidney	1	0.9	0.37	**0.87**	2.0	
					15	1.4	0.67	**1.4**	3.2	
	Mice ($C3AF_1$)	male	60 µg/g	kidney	1	1.8	0.17	**1.9**	15	
					15	2.0	0.25	**2.0**	16	
		female	60 µg/g	kidney	1	1.0	0.016	**1.3**	13	
					15	2.1	0.16	**2.2**	20	
		male	120 µg/g	kidney	1	0.2	0.0029	**0.24**	1.5	
					15	1.5	0.38	**1.5**	5.9	
		female	120 µg/g	kidney	1	2.3	0.17	**2.4**	20	
					15	7.1	1.8	**6.5**	47	
	Mice ($B6C3F_1$)	male	60 µg/g	Harderian	1	0.3	0.018	**0.41**	1.4	
					15	0.5	0.075	**0.52**	1.4	
		female	60 µg/g	Harderian	1	0.1	0.0025	**0.16**	0.74	
					15	0.8	0.35	**0.84**	2.0	
		male	120 µg/g	Harderian	1	0.4	0.13	**0.42**	0.96	
					15	0.6	0.26	**0.57**	1.2	
		female	120 µg/g	Harderian	1	0.1	0.0030	**0.18**	0.85	
					15	0.7	0.17	**0.77**	2.1	
	Mice ($C3AF_1$)	male	60 µg/g	Harderian	1	0.1	0.0023	**0.20**	1.3	
					15	0.1	0.0016	**0.18**	1.8	
		female	60 µg/g	Harderian	1	0.4	0.019	**0.52**	2.5	
					15	0.8	0.15	**0.85**	3.4	
		male	120 µg/g	Harderian	1	0.1	0.0010	**0.086**	1.0	
					15	0.3	0.0050	**0.40**	2.8	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
		female	120 µg/g	Harderian	1	0.1	0.0012	**0.094**	1.2	
					15	0.1	0.0012	**0.081**	0.90	
ENU (continued)	Mice (B6C3F$_1$)	male	60 µg/g	stomach	1	0.3	0.0091	**0.34**	2.4	
					15	1.9	0.61	**1.82**	8.7	
		female	60 µg/g	stomach	1	0.2	0.0083	**0.26**	1.1	
					15	0.2	0.0072	**0.24**	1.0	
		male	120 µg/g	stomach	1	0.2	0.0059	**0.20**	0.90	
					15	1.2	0.50	**1.2**	2.9	
		female	120 µg/g	stomach	1	0.6	0.19	**0.60**	1.5	
					15	1.6	0.67	**1.6**	3.7	
	Mice (C3AF$_1$)	male	60 µg/g	stomach	1	0.0	0.0009	**0.063**	0.51	
					15	0.3	0.023	**0.41**	1.3	
		female	60 µg/g	stomach	1	0.8	0.085	**0.89**	3.5	
					15	1.1	0.19	**1.1**	4.5	
		male	120 µg/g	stomach	1	0.2	0.010	**0.19**	0.56	
					15	0.7	0.32	**0.70**	1.5	
		female	120 µg/g	stomach	1	0.4	0.14	**0.46**	1.2	
					15	0.6	0.24	**0.64**	1.5	
NMU	Mice (BC3F$_1$)	male	50 µg/g	lung adenomas	1	3.4	1.3	**3.3**	9.3	Terracini and Testa (1970)
		female	50 µg/g	lung adenomas	1	6.3	2.4	**6.0**	23	
		male	50 µg/g	lymphosarcoma	1	2.5	1.1	**2.4**	6.4	
		female	50 µg/g	lymphosarcoma	1	1.1	0.49	**1.1**	2.4	
		male	50 µg/g	hepatoma	1	35	6.5	**32**	324	
		female	50 µg/g	hepatoma	1	0.3	0.0023	**0.39**	13	
		male	50 µg/g	renal adenoma	1	0.9	0.0093	**1.2**	13	
		female	50 µg/g	renal adenoma	1	1.3	0.0081	**1.7**	33	
		male	50 µg/g	forestomach	1	0.0	0.0006	**0.039**	0.52	
		female	50 µg/g	forestomach	1	0.1	0.0027	**0.15**	0.69	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency				Reference
						Unweighted geometric mean	2.5%	Median	97.5 %	
	Mice (C3Hf/Dp)	male	25 µg/g	thymic lymphoma	1	1.9	0.048	**2.1**	23	
NMU (continued)		female	25 µg/g	thymic lymphoma	1	1.2	0.0089	**1.5**	30	
		male	25 µg/g	lung adenomas	1	1.0	0.013	**1.2**	11	
		female	25 µg/g	lung adenomas	1	0.4	0.018	**0.46**	1. 7	
		male	25 µg/g	liver tumor	1	0.2	0.0016	**0.21**	4.6	
		female	25 µg/g	liver tumor	1	0.3	0.0026	**0.39**	4.4	
		male	25 µg/g	Stomach	1	0.5	0.0045	**0.67**	6.8	
		female	25 µg/g	Stomach	1	0.3	0.0046	**0.43**	3.8	
				ovarian	1	0.1	0.0014	**0.17**	3.5	
				uterine/vaginal	1	8.6	1.1	**8.1**	97	
		male	50 µg/g	thymic lymphoma	1	7.9	3.1	**7.4**	30	
		female	50 µg/g	thymic lymphoma	1	3.1	1.3	**3.0**	7.8	
		male	50 µg/g	lung adenomas	1	0.04	0.0008	**0.058**	0.45	
		female	50 µg/g	lung adenomas	1	0.1	0.0012	**0.084**	0.53	
		male	50 µg/g	liver tumor	1	0.2	0.0021	**0.33**	7.8	
		female	50 µg/g	liver tumor	1	0.1	0.0011	**0.13**	4.5	
		male	50 µg/g	Stomach	1	0.01	0.0003	**0.013**	0.12	
		female	50 µg/g	Stomach	1	0.1	0.0022	**0.15**	0.96	
				ovarian	1	0.0	0.0003	**0.014**	0.14	
				uterine/vaginal	1	0.0	0.0005	**0.034**	0.46	
		male	50 µg/g	thymic lymphoma	21	4.3	1. 6	**4.1**	17	
		female	50 µg/g	thymic lymphoma	21	1.0	0.39	**1.0**	2.6	
		male	50 µg/g	lung adenomas	21	0.1	0.0022	**0.22**	1.1	
		female	50 µg/g	lung adenomas	21	0.7	0.30	**0.75**	1.7	

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency: Unweighted geometric mean	2.5%	Median	97.5 %	Reference
		male	50 µg/g	liver tumor	21	0.1	0.0013	**0.15**	4.3	
		female	50 µg/g	liver tumor	21	0.9	0.0051	**1.4**	23	
NMU (continued)		male	50 µg/g	stomach	21	0.1	0.001	**0.08**	0.64	
		female	50 µg/g	stomach	21	1.8	0.77	**1.8**	4.7	
				ovarian	21	0.0	0.0007	**0.055**	0.97	
				uterine/vaginal	21	1.7	0.59	**1.7**	6.4	
Urethane	Mice (Swiss)	male	1 mg/g	liver	1	24	4.4	**21**	220	Chieco-Bianchi et al. (1963)
		female	1 mg/g	liver	1	0.4	0.0044	**0.54**	13	
		male	1 mg/g	liver	5	14	2.4	**13**	137	
		female	1 mg/g	liver	5	1.2	0.017	**1.4**	26	
		male	1 mg/g	liver	20	0.2	0.0018	**0.28**	10	
		female	1 mg/g	liver	20	0.1	0.0011	**0.12**	4.8	
		both	1 mg/g	skin	1	0.2	0.0027	**0.32**	5.4	
Urethane + croton oil	Mice (Swiss)	both	1 mg/g	skin	1	2.9	1.2	**2.8**	8.2	
Urethane	Rats (MRC Wistar-derived)	male/ female	16%×6	neurilemmomas	1	0.2	0.0028	**0.33**	4.5	Choudari Kommineni et al. (1970)
		male/ female	16%×6	neurilemmomas	28	0.4	0.0045	**0.51**	6.3	
		male/ female	16%×6	liver	1	7.9	1.4	**7.1**	82	
		male/ female	16%×6	liver	28	0.2	0.0026	**0.4**	11.7	
		male/ female	16%×6	thyroid	1	0.0	0.0006	**0.039**	0.67	
		male/ female	16%×6	thyroid	28	0.1	0.0011	**0.1**	1.5	
	Mice (Swiss)	male/ female	1 mg/g	lung	1	15	1.2	**11**	997	De Benedictis et al. (1962)
	Mice (Swiss)			leukemia		6.7	1.7	**6.1**	45	Fiore-Donati et al.

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency: Unweighted geometric mean	2.5%	Median	97.5 %	Reference
						5.1	1.1	**4.7**	38	(1962)
Urethane (continued)	Mice ($B6AF_1/J$)	male	1 mg/g	liver	21	5.1	1.4	**4.7**	30	Klein (1966)
		female	1 mg/g	liver	21	0.2	0.0019	**0.26**	6.0	
				Harderian gland	1	0.3	0.0021	**0.33**	11	
					7	0.3	0.0021	**0.33**	11	
					14	0.6	0.0044	**0.85**	20	
		male	1 mg/g	Harderian gland	21	0.3	0.0024	**0.41**	13	
		male	1 mg/g	forestomach	1	0.1	0.0009	**0.079**	1.9	
		female	1 mg/g	forestomach	1	0.4	0.0028	**0.49**	11	
		male	1 mg/g	forestomach	7	0.1	0.0017	**0.19**	3.5	
		female	1 mg/g	forestomach	7	0.1	0.0013	**0.16**	5.0	
		male	1 mg/g	forestomach	14	0.2	0.0018	**0.21**	3.9	
		female	1 mg/g	forestomach	14	0.8	0.0056	**1.1**	18	
		male	1 mg/g	forestomach	21	0.1	0.0008	**0.072**	1.7	
		female	1 mg/g	forestomach	21	0.2	0.0015	**0.2**	6.3	
				lung	1	1.0	0.36	**0.95**	2.5	
		male	1 mg/g	lung	14	0.8	0.26	**0.8**	2.3	
		female	1 mg/g	lung	14	0.4	0.16	**0.45**	1.1	
					21	0.9	0.31	**0.86**	2.4	
	Mice (C3H/f)	male	1 mg/g	liver	1	14	4.0	**12**	81	Liebelt et al. (1964)
		female	1 mg/g	liver	1	16	3.2	**15**	155	
		male	1 mg/g	lung	1	5.9	1.7	**5.6**	28	
		female	1 mg/g	lung	1	22	4.5	**20**	203	
		male	1 mg/g	reticular tissue	1	2.0	0.023	**2.3**	38	
		female	1 mg/g	reticular tissue	1	8.6	2.3	**7.7**	60	
	Mice (Swiss)		1 mg/g	pulmonary adenomas	2 vs 4 weeks	14	1.1	**10.1**	965	Rogers (1951)

Table 6. Ratio of early-life to adult cancer potencies for studies with acute exposures of juveniles and adult animals to carcinogens with a mutagenic mode of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Day	Ratio of juvenile to adult potency: Unweighted geometric mean	2.5%	Median	97.5 %	Reference
			1 mg/g	pulmonary adenomas	2 vs 6 weeks	16	1.3	**11.3**	1025	
Urethane (continued)			1 mg/g	pulmonary adenomas	2 vs 8 weeks	19	1.6	**13.3**	1126	
			1 mg/g	pulmonary adenomas	2 vs 10 weeks	21	1.9	**14.5**	1168	
			0.25 mg/g	adenomas	3 vs 8 weeks	7.1	2.3	**6.7**	29	
			0.5 mg/g	adenomas	3 vs 8 weeks	0.7	0.29	**0.67**	1.6	
			1.0 mg/g	adenomas	3 vs 8 weeks	0.7	0.28	**0.68**	1.6	

* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action*

Compound	Species (strain)	Sex	Dose	Tumor	Unweightedg eometric mean	2.5%	Median	97.5%	Reference
Mutagenic compounds									
DEN	Rats (Colworth)		multiple	liver	2.8	0.0093	**5.6**	23	Peto et al. (1984)
				esophagus	0.18	0.0015	**0.23**	4.8	
Safrole	Mice ($B6C3F_1$)	male		liver	50	3.7	**50**	253	Vesselinovitch et al. (1979b)
		female		liver	4.0	0.007	**4.0**	23	
Urethane	Mice ($B6AF_1$/J)	male	2.5 mg/pup	liver	79	0.36	**102**	1,064	Klein (1966)
		female	2.5 mg/pup	liver	0.47	0.0022	**0.55**	42	
Nonmutagenic compounds									
DDT	Mice ($B6C3F_1$)			liver	23	0.0023	**0.58**	23	Vesselinovitch et al. (1979a)
Dieldrin	Mice ($B6C3F_1$)			liver	91	0.014	**14**	91	Vesselinovitch et al. (1979a)
DPH	Rats (F344/N)	male	630:800	liver	0.31	0.0019	**0.37**	18	Chhabra et al. (1993b)
			630:2,400	liver	0.36	0.0021	**0.45**	17	
		female	630:800	liver	0.33	0.0019	**0.39**	21	
			630:2,400	liver	0.33	0.0019	**0.39**	21	
	Mice ($B6C3F_1$)	male	210:100	liver	0.71	0.0028	**0.93**	49	
			210:300	liver	14	0.03	**23**	214	
		female	210:200	liver	0.32	0.002	**0.42**	13	
			210:600	liver	0.35	0.0023	**0.53**	8.8	
ETU	Rats (F344/N)	male	90:83	thyroid	0.23	0.0017	**0.3**	7.3	Chhabra et al. (1992)
			90:250	thyroid	9.1	1.1	**10.5**	27	
		female	90:83	thyroid	0.37	0.0021	**0.46**	19	
			90:250	thyroid	0.61	0.0034	**1.1**	10	

Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Unweighted geometric mean	2.5%	Median	97.5%	Reference
ETU (continued)	Mice ($B6C3F_1$)	male	330:330	liver	0.37	0.0022	**0.5**	14	
			330:1,000	liver	0.48	0.0027	**0.75**	12	
		female	330:330	liver	0.33	0.0023	**0.5**	7.8	
			330:1,000	liver	0.42	0.0025	**0.65**	11	
		male	330:330	thyroid	0.44	0.0022	**0.52**	34	
			330:1,000	thyroid	0.63	0.0035	**1.12**	10	
		female	330:330	thyroid	5.2	0.011	**10**	108	
			330:1,000	thyroid	0.18	0.0016	**0.24**	4.2	
		male	330:330	pituitary	0.40	0.0021	**0.47**	32	
			330:1,000	pituitary	0.18	0.0015	**0.22**	5.7	
		female	330:330	pituitary	0.21	0.0016	**0.26**	10	
			330:1,000	pituitary	0.27	0.0019	**0.36**	9.0	
PBB	Rats (F344/N)	male	10:10	liver	0.39	0.0023	**0.56**	13	Chhabra et al. (1993a)
			10:30	liver	0.18	0.0016	**0.25**	4.3	
		female	10:10	liver	36	15	**36**	86	
			10:30	liver	3.1	0.023	**4.6**	22	
		male	10:10	mononuclear cell leukemia	0.51	0.0025	**0.69**	23	
		male	10:30	mononuclear cell leukemia	0.77	0.0031	**1.1**	35	
		female	10:10	mononuclear cell leukemia	0.54	0.0026	**0.74**	24	
		female	10:30	mononuclear cell leukemia	0.34	0.0021	**0.45**	15	
	Mice ($B6C3F_1$)	male	30:30	liver	8.9	0.015	**12.2**	1,076	
		female	30:30	liver	4.4	0.0075	**6.2**	786	
		male	10:10	liver	0.15	0.0014	**0.2**	3.9	

Table 7. Ratio of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic or nonmutagenic modes of action (continued)

Compound	Species (strain)	Sex	Dose	Tumor	Unweighted geometric mean	2.5%	Median	97.5%	Reference
		female	10:10	liver	0.29	0.0021	**0.43**	7.0	

* The 2.5% and 97.5% are percentiles of the posterior distribution. For a Bayesian distribution, these percentiles function in a manner similar to the 95% confidence limits for other types of statistical analyses.

Table 8. Summary of quantitative estimates of ratio of early-life to adult cancer potencies

Dose	Tissue	Number of chemicals	Inverse-weighted geometric mean ratio	Unweighted Minimum	Unweighted Maximum	Number of ratios	Percentage >1
Chemicals with mutagenic mode of action							
Repeated		4	10.5	0.12	111	45	42
Lifetime		3	8.7	0.18	79	6	67
	Combined repeated and lifetime	**6**	**10.4**	**0.12**	**111**	**51**	**45**
Acute	**Combined**	11	1.5	0.01	178	268	55
	Forestomach	3	0.076	0.01	1.9	32	16
	Harderian	2	0.48	0.06	0.8	20	0.0
	Kidney	2	1.6	0.17	7.1	18	78
	Leukemia	1	5.9	5.1	6.7	2	100
	Liver	5	8.1	0.10	40	70	77
	Lung	7	1.1	0.04	178	77	56
	Lymph	2	1.8	1.1	2.7	3	100
	Mammary (wk 5 vs wk 26)	1	7.1	NA	NA	1	100
	Mammary (wk 2 vs wk 5–8 or 26)	1	0.071	NA	NA	2	0
	Nerve	2	2.3	0.24	64	8	75
	Nerve (Day 1 comparison)	2	10	0.24	64	3	67
	Ovarian	1	0.033	0.01	0.13	3	0
	Reticular tissue	1	6.5	1.96	8.6	2	100
	Thymic lymphoma	1	2.8	1.01	7.9	6	100
	Thyroid	1	0.05	0.03	0.08	2	0
	Uterine/vaginal	1	1.6	0.03	8.6	3	67
	Day 1	7	1.7	0.01	178	127	55
	Day 15	3	1.5	0.06	52	74	65
Chemicals with nonmutagenic mode of action							
Repeated		6	2.2	0.06	13	22	27
Lifetime		5	3.4	0.15	36	38	21

Table 9. Excess Relative Risk (ERR) estimates for cancer incidence from Life Span Study (Japanese survivors)[a]

Site	Average ERR at 1 Sv	
	<20[b]	>20[b]
Stomach	0.74	0.24
Colon	0.62	0.7
Liver	1.3	0.31
Lung	0.57	1.1
Bone and connective tissue	11	0.42
Skin	5.4	0.39
Breast	3.3	0.98
Urinary bladder	0.71	0.79
Leukemia	6.1	3.7

[a] Information extracted from tables in UNSCEAR, Annex I (2000).
[b] Age at exposure.

Table 10. Excess Relative Risk (ERR) estimates for incidence of thyroid cancer from Life Span Study[a]

Age at exposure	Average ERR at 1 Sv (No. cases)
0–9 yr	10.25 (24)
10–19 yr	4.5 (35)
20–29 yr	0.10 (18)
>30 yr	0.04 (55)

[a] Information extracted from tables in UNSCEAR, Annex I (2000).

Table 11. Coefficients for the Revised Methodology mortality risk model (from U.S. EPA, 1999)[a]

Cancer type	Risk model type[b]	Age group				
		0–9	10–19	20–29	30–39	40+
Male:						
Stomach	R	1.223	1.972	2.044	0.3024	0.2745
Colon	R	2.290	2.290	0.2787	0.4395	0.08881
Liver	R	0.9877	0.9877	0.9877	0.9877	0.9877
Lung	R	0.4480	0.4480	0.0435	0.1315	0.1680
Bone	A	0.09387	0.09387	0.09387	0.09387	0.09387
Skin	A	0.06597	0.06597	0.06597	0.06597	0.06597
Breast	R	0.0	0.0	0.0	0.0	0.0
Ovary	R	0.0	0.0	0.0	0.0	0.0
Bladder	R	1.037	1.037	1.037	1.037	1.037
Kidney	R	0.2938	0.2938	0.2938	0.2938	0.2938
Thyroid	A	0.1667	0.1667	0.1667	0.1667	0.1667
Leukemia	R	982.3	311.3	416.6	264.4	143.6
Female:						
Stomach	R	3.581	4.585	4.552	0.6309	0.5424
Colon	R	3.265	3.265	0.6183	0.8921	0.1921
Liver	R	0.9877	0.9877	0.9877	0.9877	0.9877
Lung	R	1.359	1.359	0.1620	0.4396	0.6047
Bone	A	0.09387	0.09387	0.09387	0.09387	0.09387
Skin	A	0.06597	0.06597	0.06597	0.06597	0.06597
Breast	R	0.7000	0.7000	0.3000	0.3000	0.1000
Ovary	R	0.7185	0.7185	0.7185	0.7185	0.7185
Bladder	R	1.049	1.049	1.049	1.049	1.049
Kidney	R	0.2938	0.2938	0.2938	0.2938	0.2938
Thyroid	A	0.3333	0.3333	0.1667	0.1667	0.1667
Leukemia	R	1,176	284.9	370.06	178.8	157.1

[a] The coefficients were derived using several models applied to data from A-bomb survivors and selected medical exposures.
[b] A = absolute risk with coefficient units of 10^{-4} (Gy y)$^{-1}$; R= relative risk with coefficient units of Gy^{-1}.

REFERENCES

Anderson, LM; Diwan, BA; Fear, NT; et al. (2000) Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 108(Suppl 3):573−594.

Barton, HA; Cogliano, VJ; Flowers, L; Valcovic, L; Setzer, RW; Woodruff, TJ. (2005). Assessing susceptibility from early-life exposure to carcinogens. Environ Health Perspect (in press).

Birch, JM; Blair, V; Kelsey, AM; et al. (1998) Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. Oncogene 17:1061−1068.

Birnbaum, LS; Fenton, SE. (2003) Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect 111:389−394.

Bosland, MC. (1996) Hormonal factors in carcinogenesis of the prostate and testis in humans and in animal models. Prog Clin Biol Res 394:309−352.

Carlin, BP; Louis, TA. (2000). Bayes and empirical Bayes methods for data analysis: 2nd ed. Boca Raton, Fl: Chapman and Hall/CRC.

Carthew, P; Rich, KJ; Martin, EA; et al. (1995) DNA damage as assessed by ^{32}P-postlabelling in three rat strains exposed to dietary tamoxifen: the relationship between cell proliferation and liver tumor formation. Carcinogenesis 16:1299−1304.

Carthew, P; Edwards, RE; Nolan, BM; et al. (2000) Tamoxifen induces endometrial and vaginal cancer in rats in the absence of endometrial hyperplasia. Carcinogenesis 21:793−797.

Carthew, P; Edwards, RE; Nolan, BM; et al. (1996) Tamoxifen associated uterine pathology in rodents: relevance to women. Carcinogenesis 17:1577−1582.

Cattley, RC; Marsman, DS; Popp, JA. (1991) Age-related susceptibility to the carcinogenic effect of the peroxisome proliferator WY-14,643 in rat liver. Carcinogenesis 12:469−473.

Chhabra, RS; Eustis, S; Haseman, JK; et al. (1992) Comparative carcinogenicity of the ethylene thiourea with or without perinatal exposure in rats and mice. Fundam Appl Toxicol 18:405−417.

Chhabra, RS; Bucher, JR; Haseman, JK; et al. (1993a) Comparative carcinogenicity of polybrominated biphenyls with or without perinatal exposure in rats and mice. Fundam Appl Toxicol 21:451−460.

Chhabra, RS; Bucher, JR; Haseman, JK; et al. (1993b) Comparative carcinogenicity of 5,5-diphenylhydantoin with or without perinatal exposure in rats and mice. Fundam Appl Toxicol 21:174−186.

Chieco-Bianchi, L; De Benedictis, G; Tridente, G; et al. (1963) Influence of age on susceptibility to liver carcinogenesis and skin initiating action by urethane in Swiss mice. Br J Cancer 17:672−680.

Choudari Kommineni, VR; Greenblatt, M; Vesselinovitch, SD; et al. (1970) Urethan carcinogenesis in rats: importance of age and dose. J Natl Cancer Inst 45(4):687−696.

Cimino, MC. (2001) New OECD genetic toxicology guidelines and interpretation of results. In: Choy, WN, ed. Genetic toxicology and cancer risk assessment. New York, NY: Marcel Dekker, pp. 223−248.

Cohen, SM; Garland, EM; Cano, M; et al. (1995) Effects of sodium ascorbate, sodium saccharin and ammonium chloride on the male rat urinary bladder. Carcinogenesis 16(11):2743−2750.

Cohen, SM; Anderson, TA; de Oliveira, LM; et al. (1998) Tumorogenicity of sodium ascorbate in male rats. Cancer Res 58:2557−2561.

Covelli, V; Di, MV; Bassani, B; et al. (1984) Influence of age on life shortening and tumor induction after x-ray and neutron irradiation. Radiat Res 100:348−364.

Dearfield, KL; Auletta, AE; Cimino, MC; et al. (1991) Considerations in the U.S. Environmental Protection Agency's testing approach for mutagenicity. Mutat Res 258:259−283.

Dearfield, KL; McCarroll, NE; Protzel, A; et al. (1999) A survey of EPA/OPP and open literature on selected pesticide chemicals II. Mutagenicity and carcinogenicity of selected chloroacetanilides and related compounds. Mutat Res 443:183−221.

De Benedictis, G; Maiorano, G; Chieco-Bianchi, L., et al. (1962) Lung carcinogenesis by urethane in newborn, suckling, and adult Swiss mice. Br J Cancer 16:686−689.

Della Porta, G; Terracini, B. (1969) Chemical carcinogenesis in infant animals. Prog Exp Tumor Res 11:334−363.

Delongchamp, RR; Mabuchi, K; Yoshimoto,Y; et al. (1997) Cancer mortality among atomic bomb survivors exposed in utero or as young children: October 1950-May 1992. Radiat Res 147:385−395.

Di, MV; Coppola, M; Rebessi, S; et al. (1990) Age-related susceptibility of mouse liver to induction of tumors by neutrons. Radiat Res 124:227−234.

Diwan, BA; Kasprzak, KS; Rice, JM. (1992) Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. Carcinogenesis 13(8):1351−1357.

Diwan, BA; Riggs, CW; Logsdon, D; et al. (1999) Multiorgan transplacental and neonatal carcinogenicity of 3'azido-deoxythymidine in mice. Toxicol Appl Pharmacol 161:82−99.

Drew, RT; Boorman, GA; Haseman, JK; et al. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol Appl Pharmacol 68:120−130.

Druckery, H. (1973) Chemical structure and action in transplacental carcinogenesis and teratogenesis. IARC Sci Pub 4:45−57.

Fenton, SE; Davis, CC. (2002) Atrazine exposure in utero increases dimethylbenz a anthracene-induced mammary tumor incidence in long evans offspring. Toxicol Sci 66(1−2):185. "The Toxicologist, Abstracts of the 41st Annual Meeting of the Society of Toxicology." (Abstract 903).

Fiore-Donati, L; De Benedictis, G; Chieco-Bianchi, L; et al. (1962) Leukaemogenic activity of Urethan in Swiss and AKR mice. Nature 190:134−139.

Flammang, TJ; Von Tungeln, LS; Kadlubar, FF; et al. (1997) Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Regul Toxicol Pharmacol 26:230−240.

Fujii, K. (1991) Evaluations for the newborn mouse model for chemical tumorigenesis. Carcinogenesis 8:1409−1415.

Gass, GH; Coats, D; Graham, N. (1964) Carcinogenic dose-response curve to oral diethylstilbestrol. J Natl Cancer Inst 33:971−977.

Ginsberg, GL. (2003) Assessing cancer risks from short-term exposures in children. Risk Anal 23:19−34.

Ginsberg, G; Hattis, D; Sonawane, B; et al. (2002) Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66:185−200.

Goddard, MJ; Krewski, D. (1995) The future of mechanistic research in risk assessment: where are we going and can we get there from here? Toxicology 102:53−70.

Greenman, DL; Highman, B; Chen, J; et al. (1990) Estrogen-induced thyroid follicular cell adenomas in C57Bl/6 mice. J Toxicol Environ Health 29:269−278.

Grufferman, S. (1998) Methodologic approaches to studying environmental factors in childhood cancer. Environ Health Perspect 106(Suppl 3):881−886.

Hale, GA; Marina, NM; Johnes-Wallace, D; et al. (1999) Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 21:115−122.

Halmes, NC; Roberts, SM; Tolson, JK; et al. (2000) Reevaluating cancer risk estimates for short-term exposure scenarios. Toxicol Sci 58:32−42.

Hard, GC. (1979) Effect of age at treatment on incidence and type of renal neoplasm induced in the rat by a single dose of dimethylnitrosamine. Cancer Res 39:4965−4970.

Hartis, D; Goble, R; and Chu, M. (2005) Age-related differences in susceptibility to carcinogenesis II. Approaches for application and uncertainty analyses for individual genetically acting carcinogens. Environ Health Perspect 113:509-516..

Hatch, EE; Palmer, JR; Titus-Ernstoff, L; et al. (1998) Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 280:630−634.

Hayashi, M; MacGregor, JT; Gatehouse, DG; et al. (2000) In vivo rodent erythrocyte micronucleus assay II. Some aspects of protocol design including repeated treatments, integration with toxicity testing, and automated scoring. Environ Mol Mutagen 35:234−252.

Holladay SD, Smialowicz RJ. 2000. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. Environ Health Perspect 108 Suppl 3:463-473.

Holsapple MP, West LJ, Landreth KS. 2003. Species comparison of anatomical and functional immune system development. Birth Defects Res B Dev Reprod Toxicol 68(4):321-334.

Israel, MA. (1995) Molecular biology of childhood neoplasms. In: Mendelsohn, J; Howley, PM; Israel, MA; et al.; eds. The molecular basis of cancer. Saunders; Philadelphia, PA: pp. 294−316.

Jurgelski, Jr, W; Hudson, P; Falk, HL. (1979) Tissue differentiation and susceptibility to embryonal tumor induction by ethylnitrosourea in the opossum. NCI Monograph 51: 123−158.

Kaye, AM; Trainin, N. (1966) Urethan carcinogenesis and nucleic acid metabolism: Factors influencing lung adenoma induction. Cancer Res 26:2206−2212.

Klein, M. (1959) Development of hepatomas in inbred albino mice following treatment with 20-Methylcholanthrene. Cancer Res 19:1109−1113.

Klein, M. (1966) Influence of age on induction with urethan of hepatomas and other tumors in infant mice. J Natl Cancer Inst 36(6):1111−1120.

Kraupp-Grasl, B; Huber, W; Taper, H; et al. (1991) Increased susceptibility of aged rats to hepatocarcinogenesis by the peroxisome proliferator nafenopin and the possible involvement of altered liver foci occurring spontaneously. Cancer Res 51:666−671.

Kushner, BH; Heller, G; Cheung, NK; et al. (1998) High risk of leukemia after short-term dose-intensive chemotherapy in young patients with solid tumors. J Clin Oncol 16:3016−3020.

Laib, RJ; Bolt, HM; Cartier, R; et al. (1989) Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol Lett 45:231−239.

Larson, RA; LeBeau, MM; Vardiman, JW; et al. (1996) Myeloid leukemia after hematotoxins. Environ Health Perspect 104(Suppl 6):1303−1307.

Laurenzana, EM; Weis, CC; Bryant, CW; et al. (2002) Effect of dietary administration of genistein, nonylphenol or ethinyl estradiol on hepatic testosterone metabolism, cytochrome P-450 enzymes, and estrogen receptor alpha expression. Food Chem Toxicol 40:53−63.

Law, LW. (1940) The production of tumors by injection of a carcinogen into the amniotic fluid of mice. Science 91:96−97.

Liebelt, RA; Leibelt, AG; Lane, M. (1964) Hormonal influences on urethan carcinogenesis in C3H/f mice. Cancer Res 24:1869−1879.

Lindahl, T; Klein, G; Reedman, BM; et al. (1974) Relationship between Epstein-Barr virus (EBV) DNA and the EBV-determined nuclear antigen (EBNA) in Burkitt lymphoma biopsies and other lymphoproliferative malignancies. Int J Cancer 13:764-772.

Maekawa, A; Mitsumori, K. (1990) Spontaneous occurrence and chemical induction of neurogenic tumors in rats−influence of host factors and specificity of chemical structure. Crit Rev Toxicol 20(4):287−310.

Mahoney, FJ. (1999) Update on diagnosis, management, and prevention of hepatitis B virus infection. Clin Microbiol Rev 12:351−366.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. Environ Health Perspect 41:3−29.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1984) Experimental research on vinyl chloride carcinogenesis. In: Maltoni, C; Mehlaman, MA; eds. Archives of Research on Industrial Carcinogenesis. Vol. II. Princeton, NJ: Princeton Scientific Publishing.

McCarroll, NE; Protzel, A; Ioannou, Y; et al. (2002) A survey of EPA/OPP and open literature on selected pesticide chemicals. III. Mutagenicity and carcinogenicity of benomyl and carbendazim. Mutat Res 512:1−35.

McClain, R; Keller, D; Casciano, D; et al. (2001) Neonatal mouse model: review of methods and results. Toxicol Pathol 29(Suppl):128−137.

McConnell, EE. (1992) Comparative response in carcinogenesis bioassay as a function of age at first exposure. In: Guzelian, P; Henry, CJ; Olin, SS; eds. Similarities and difference between children and adults: implications for risk assessment. Washington, DC: ILSI Press; pp. 66−78.

McCurdy, T; Glen, G; Smith, L; et al. (2000) The National Exposure Research Laboratory's consolidated human activity database. J Expo Anal Environ Epidemiol 10:566−578.

Meranze, DR; Gruenstein, M; Shimkin, MB. (1969) Effect of age and sex on the development of neoplasms in Wistar rats receiving a single intragastric instillation of 7,12-dimethylbenz(a)anthracene. Int J Cancer 4:480−486.

Miller, MD; Marty, MA; Arcus, A; et al. (2002) Differences between children and adults: implications for risk assessment at California EPA. Int J Toxicol 21:403−418.

Morinello, EJ; Ham, AJL; Ranasinghe, A; et al. (2002a) Molecular dosimetry and repair of N2,3-ethenoguanine in rats exposed to vinyl chloride. Cancer Res 62:5189−5195.

Morinello, EJ; Koc, H; Ranasinghe, A; et al. (2002b) Differential induction of N(2),3-ethenoguanine in rat brain and liver after exposure to vinyl chloride. Cancer Res 62(18):5183−5188.

Murdoch, DJ; Krewski, D; Wargo, J. (1992) Cancer risk assessment with intermittent exposure. Risk Anal 12:569−577.

Naito, M.; Naito, Y; Ito, A. (1981) Effect of age at treatment on the incidence and location of neurogenic tumors induced in Wistar rats by a single dose of N-ethyl-N-nitrosourea. Gann 72(4):569−577.

Newbold, RR; Bullock, BC; McLachlan, JA. (1990) Uterine adenocarcinoma in mice following developmental treatment with estrogens: a model for hormonal carcinogenesis. Cancer Res 50:7677−7681.

Newbold, RR; Jefferson, WN; Padilla-Burgos, E; et al. (1997) Uterine carcinoma in mice treated neonatally with tamoxifen. Carcinogenesis 18:2293−2298.

Newbold, RR; Hanson, RB; Jefferson, WN; et al. (1998) Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 19:1655−1663.

Newbold, RR; Banks, EP; Bullock, B; et al. (2001) Uterine adenocarcinoma in mice treated neonatally with genistein. Cancer Res 61:4325−4328.

NRC (National Research Council). (1990) Health effects of exposure to low levels of ionizing radiation. Beir V. Committee on the Biological Effects of Ionizing Radiation. Washington, DC: National Academy Press. Available online at http://www.nap.edu/catalog/1224.html?se_side.

NRC (National Research Council). (1993). Pesticides in the diets of infants and children. Committee on Pesticides in the Diets of Infants and Children. Commission on Life Sciences. Washington, DC: National Academy Press. Available online at http://www.nap.edu/catalog/2126.html?se_side.

NRC (National Research Council). (1994). Science and judgment in risk assessment. Committee on Risk Assessment of Hazardous Air Pollutants. Commission on Life Sciences. Washington, DC: National Academy Press. Available online at http://www.nap.edu/catalog/2125.html.

NTP (National Toxicology Program). (1983) Carcinogenesis bioassay of L-ascorbic acid (Vitamin C) (CAS No. 50-81-7) in F344/N rats and B6C3F1 mice (feed study). Research Triangle Park, NC: National Toxicology Program; TR−247.

NTP (National Toxicology Program). (1999) Toxicology and carcinogenesis studies of AZT and AZT/gamma-interferon in $B6C3F_1$ mice (gavage studies). Research Triangle Park, NC: National Toxicology Program; TR−469.

Nyandoto, P; Muhonen, T; Joensuu, H. (1998) Second cancer among long-term survivors from Hodgkin's disease. Int J Radiat Oncol Biol Phys 42:373−378.

OECD (Organization for Economic Cooperation and Development). (1998) OECD guidelines for the testing of chemicals. Paris, France: Organization for Economic Cooperation and Development.

Paulsen, JE; Steffensen, IL; et al. (2003) Age-dependent susceptibility to azoxymethane-induced and spontaneous tumorigenesis in the *Min*/ + mouse. Anticancer Res 23:259−265.

Peto, R; Gray, R; Brantom, P; et al. (1984) Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3,6, or 20 weeks) and of species (rats, mice, or hamsters). Lyon, France: IARC Sci Publ; publication no. 57:627−665.

Pietra, G; Rappaport, H; Shubik, P. (1961) The effects of carcinogenic chemicals in newborn mice. Cancer 14:308−317.

Preston, DL; Pierce, DA; Shimizu, Y. (2000) Age-time patterns for cancer and noncancer excess risks in the atomic bomb survivors. Radiat Res 154:733−734.

R Development Core Team (2003). R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; ISBN 3-900051-00-3. Available online at http://www.R−project.org.

Renwick, AG. (1998) Toxicokinetics in infants and children in relation to the ADI and TDI. Food Addit Contam 15:S17−S35.

Rice, JM; Ward, JM. (1982) Age dependence of susceptibility to carcinogenesis. Ann NY Acad Sci 381:274−289.

Ries, LA; Kosary, CL; Hanke, BF; et al. (eds.) (1999). SEER Cancer Statistics Review 1993-1998. Bethesda, MD: National Cancer Institute.

Robboy, SJ; Noller, KL; O'Brien, P; et al. (1984) Increased incidence of cervical and vaginal dysplasia in 3,980 diethylstilbestrol-exposed young women: experience of the National Collaborative Diethylstilbestrol Adenosis Project. JAMA 252:2979−2983.

Rogers, S. (1951) Age of the host and other factors affecting the production with urethane of pulmonary adenomas in mice. J Exp Med 93:426−449.

Russo, J; Wilgus, G; Russo, IH. (1979) Susceptibility of the mammary gland to carcinogenesis: I Differentiation of the mammary gland as determinant of tumor incidence and type of lesion. Am J Pathol 96(3):721−736.

Sasaki, S; Kasuga, T; Sato, F; et al. (1978) Induction of hepatocellular tumor by x-ray irradiation at perinatal stage of mice. Gann 69:451−452.

Scheuplein, R; Charnley, G; Dourson, M. (2002) Differential sensitivity of children and adults to chemical toxicity. I: biological basis. Regul Toxicol Pharmacol 35:429−447.

Silberstein, GB. (2001) Tumour-stromal interactions: role of the stroma in mammary development. Breast Cancer Res 3:218−223.

Slikker W, 3rd, Mei N, Chen T. 2004. N-ethyl-N-nitrosourea (ENU) increased brain mutations in prenatal and neonatal mice but not in the adults. Toxicol Sci 81(1):112-120.

Terracini, B; Testa, M. (1970) Carcinogenicity of a single administration of N-nitrosomethylurea: a comparison of newborn and 5-week-old mice and rats. Br J Cancer 24(3):588−598.

Terracini, B; Testa, MC; Cabral, JR; et al. (1976) The roles of age at treatment and dose in carcinogenesis in C3Hf/Dp mice with a single administration of N-nitroso-N-methylurea. Br J Cancer 33(4):427−439.

Thompson, DE; Mabuchi, K; Ron, E; et al. (1994) Cancer incidence in atomic bomb survivors, Part II: solid tumors, 1958-1987. Radiat Res 137:S17−S67.

Tomlinson, IP; Hampson, R; Karran, P; et al. (1997) DNA mismatch repair in lymphoblastoid cells from hereditary non-polyposis colorectal cancer (HNPCC) patients is normal under conditions of rapid cell division and increased mutational load. Mutat Res 383:177−182.

Toth, B. (1968) A critical review of experiments in chemical carcinogenesis using newborn animals. Cancer Research 28:727−738.

U.S. Cancer Statistics Working Group. (2002) United States cancer statistics: 1999 incidence. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Available online at http://www.cdc.gov/cancer/npcr/uscs/.

U.S. EPA (Environmental Protection Agency). (1986) Guidelines for mutagenicity risk assessment. Federal Register 51:34006−34012. Available online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=55907.

U.S. EPA (Environmental Protection Agency). (1991) Pesticide assessment guidelines, subdivision F, hazard evaluation: human and domestic animals, series 84, mutagenicity, addendum 9. Office of Pesticides and Toxic Substances, Washington, DC; EPA-540/09- 91-122. Available from: National Technical Information Service, Springfield, VA PB91-158394.

U.S. EPA (Environmental Protection Agency). (1994) Estimating radiogenic cancer risks. Washington, DC; EPA/ 402/R-93/076. Available online at http://www.epa.gov/radiation/docs/rad−risk.pdf.

U.S. EPA (Environmental Protection Agency). (1996) Comparison of the effects of chemicals with combined perinatal and adult exposure vs adult only exposure in carcinogenesis bioassays. Office of Pesticide Programs, Washington, DC. Available online at http://www.epa.gov/scipoly/sap/1996/index.htm.

U.S. EPA (Environmental Protection Agency). (1999) Cancer risk coefficients for environmental exposure to radionuclides. Federal Guidance Report No. 13. Washington, DC; EPA/402-R-99-001. Available online at http://www.epa.gov/radiation/assessment/pubs.html.

U.S. EPA (Environmental Protection Agency). (2000a) Atrazine health assessment: Part B: Hazard assessment and review of available studies. Office of Pollution, Pesticides, and Toxic Substandes, Washington, DC. Available online at http://www.epa.gov/scipoly/sap/2000/june27/finalpartb_atz.pdf.

U.S. EPA (Environmental Protection Agency). (2000b) Toxicological review of vinyl chloride. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC; EPA/635/R-00/004. Available online at http://www.epa.gov/iris/toxreviews/1001-tr.pdf.

U.S. EPA (Environmental Protection Agency). (2000c) Risk information for vinyl chloride. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/subst/1001.htm.

U.S. EPA (Environmental Protection Agency). (2002a) Child-specific exposure factors handbook. National Center for Environmental Assessment, Washington, DC; EPA/600/P-00/002B. Available from National Technical Information Service, Springfield, VA, and online at http://www.epa.gov/ncea.

U.S. EPA (Environmental Protection Agency). (2002b) OPPTS harmonized test guidelines, series 870 health effects test guidelines. Office of Pollution, Pesticides and Toxic Substances, Washington, DC. Available online at http://www.epa.gov/opptsfrs/OPPTS.

U.S. EPA (Environmental Protection Agency). (2004) Guidelines for carcinogen risk assessment. Risk Assessment Forum, National Center for Environmental Assessment, Washington, DC. Available online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=55907.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation (2000). Sources and effects of ionizing radiation. 2000 Report to the General Assembly, with scientific annexes. New York, NY: United Nations Scientific Committee on the Effects of Atomic Radiation. Available online at http://www.unscear.org/reports/2000_1.html.

Vesselinovitch, SD. (1983) Perinatal hepatocarcinogenesis. Biol Res Pregnancy Perinatol 4(1):22−25.

Vesselinovitch, S. D; Mihailovich, N. (1983) Kinetics of diethylnitrosamine hepatocarcinogenesis in the infant mouse. Cancer Res 43:4253−4259.

Vesselinovitch, SD; Rao, KV; Mihailovich, N; et al. (1974) Development of broad spectrum of tumors by ethylnitrosourea in mice and the modifying role of age, sex, and strain. Cancer Res 34(10):2530−2538.

Vesselinovitch, SD; Kyriazis, AP; Milailovich, N; et al. (1975a) Conditions modifying development of tumors in mice at various sites by benzo(a)pyrene. Cancer Res 35:2948−2953.

Vesselinovitch, SD; Rao, KV; Mihailovich, N. (1975b) Factors modulating benzidine carcinogenicity bioassay. Cancer Res 35(10):2814–2819.

Vesselinovitch, SD; Rao, KV; Mihailovich, N. (1979) Neoplastic response of mouse tissues during perinatal age periods and its significance in chemical carcinogenesis. NCI Mongraph 51:239–250.

Vesselinovitch, SD; Rao, KV; Mihailovich, N. (1979a) Neoplastic response of mouse tissues during perinatal age periods. NCI Mongraph 51:239–250.

Vesselinovitch, SD; Rao, KV; Mihailovich, N. (1979b) Transplacental and lactational carcinogenesis by safrole. Cancer Res 39(11):4378–4380.

Vesselinovitch, SD; Koka, M; Mihailovich, N; et al. (1984) Carcinogenicity of diethylnitrosamine in newborn, infant, and adult mice. J Cancer Res Clin Oncol 108:60–65.

Vessey, MP. (1989) Epidemiological studies of the effects of diethylstilboestrol. Lyon, France: IARC Sci Publ; publication No 96, pp. 335–348.

Waalkes, MP; Ward, JM; Diwan, BA. (2003) Transplacental carcinogenicity of inorganic arsenic in the drinking water: induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. Toxicol Appl Pharmacol 186:7–17.

Walters, MA. (1966) The induction of lung tumours by the injection of 9,10-dimethyl-1,2-benzanthracene (DMBA) into newborn suckling and young adult mice. A dose response study. Br J Cancer 20(1):148–160.

Waters, MD; Stack, HF; Jackson, MA. (1999) Short-term tests for defining mutagenic carcinogens. In: McGregor, DB; Rice, JM; Venitt, S; eds. The use of short term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Lyon, France: International Agency for Research on Cancer. Publ. No. 146, pp. 499–536.

Whysner, J; Williams, GM. (1996) Saccharin mechanistic data and risk assessment: urine composition, enhanced cell proliferation, and tumor promotion. Pharmacol Ther 71:225–252.

Zartarian, VG; Özkaynak, H; Burke, JM; et al. (2000) A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and non-dietary ingestion. Environ Health Perspect 108:505–514.

Message

From: Frye, Tony (Robert) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=58C08ABDFC1B4129A10456B78E6FC2E1-FRYE, ROBER]

Sent: 1/11/2019 4:31:47 PM

To: Lyons, Troy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=15e4881c95044ab49c6c35a0f5eef67e-Lyons, Troy]; Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Greaves, Holly [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=abcb6428b3df40a9a78b059a8ba59707-Greaves, Ho]; Ross, David P [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=119cd8b52dd14305a84863124ad6d8a6-Ross, David]; Dunlap, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=591eb15a268249dda0c05a7451f765c3-Dunlap, Dav]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bolen, Brittany [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=31e872a691114372b5a6a88482a66e48-Bolen, Brit]; Bodine, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8c2cc6086fcc44c3be6b5d32b262d983-Bodine, Sus]; Leopold, Matt (OGC) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e5cdf09a3924dada6d322c6794cc4fa-Leopold, Ma]; Palich, Christian [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=330ad62e158d43af93fcbbece930d21a-Palich, Chr]; Jackson, Ryan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=38bc8e18791a47d88a279db2fec8bd60-Jackson, Ry]; Wright, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=11616a3db06f4eceb13ea26c7e6dc1f0-Wright, Pet]

CC: Molina, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d19c1d68da1a4587866e1850f22a6ae5-Molina, Mic]; Humphreys, Hayly [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4f4a7b4aeaf143bf806b0dd5b7884324-Humphreys,]; Eby, Natasha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d5c14481f6874e3aa434b3b01a4a2a7d-Eby, Natash]; Shimmin, Kaitlyn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=becb3f33f9a14acd8112d898cc7853c6-Shimmin, Ka]; Block, Molly [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=60d0c681a16441a0b4fa16aa2dd4b9c5-Block, Moll]; Hewitt, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41b19dd598d340bb8032923d902d4bd1-Hewitt, Jam]; Abboud, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b6f5af791a1842f1adcc088cbf9ed3ce-Abboud, Mic]; Ringel, Aaron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1654bdc951284a6d899a418a89fb0abf-Ringel, Aar]; Voyles, Travis [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4c2b6c0d5ff046e7809f8cab2913bc48-Voyles, Tra]; Rodrick, Christian [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6515dbe46dae466da53c8a3aa3be8cc2-Rodrick, Ch]; Konkus, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=555471b2baa6419e8e141696f4577062-Konkus, Joh]

Subject: RE: UPDATED AW Murder Boards

Attachments: Potential Murderboard Questions for Acting-Administrator Andrew Wheeler -- Administrator Nominee.pdf

Hello All – Attached please find a bank of potential murder board questions our team assembled. We also have a hard copies available in 3442 WJCN if you would like one.

Additionally, if you plan on attending the White House murder board, don't forget to fill out the WAVES information by 5pm this afternoon:
https://events.whitehouse.gov/?rid=2WBM3PCVP3.

Let us know if you have any additional questions.

Best,
Tony

Tony Frye
Special Advisor
Office of Congressional Affairs
Environmental Protection Agency
Cell: 202.603.3225

From: Lyons, Troy
Sent: Thursday, January 10, 2019 3:06 PM
To: Wehrum, Bill <Wehrum.Bill@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Greaves, Holly <greaves.holly@epa.gov>; Ross, David P <ross.davidp@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Bodine, Susan <bodine.susan@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Palich, Christian <palich.christian@epa.gov>; Jackson, Ryan <jackson.ryan@epa.gov>; Wright, Peter <wright.peter@epa.gov>
Cc: Molina, Michael <molina.michael@epa.gov>; Humphreys, Hayly <humphreys.hayly@epa.gov>; Eby, Natasha <eby.natasha@epa.gov>; Frye, Tony (Robert) <frye.robert@epa.gov>; Shimmin, Kaitlyn <shimmin.kaitlyn@epa.gov>; Block, Molly <block.molly@epa.gov>; Hewitt, James <hewitt.james@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Ringel, Aaron <ringel.aaron@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>; Rodrick, Christian <rodrick.christian@epa.gov>; Konkus, John <konkus.john@epa.gov>
Subject: UPDATED AW Murder Boards

Per my announcement this morning—**the January 14th murder board will just be with White House staff** in order to be respectful of everyone's time.

Please let Christian if you would still like to attend and observe—he can send you the WAVES information. Due to the shutdown folks are on their own for transportation.

The January 15th murder board at EPA will just be EPA staff. The request remains the same—for each program office to pepper AW with questions related to their respective offices.

Please let me know if you have any questions.

From: Lyons, Troy
Sent: Monday, January 7, 2019 5:45 PM
To: Wehrum, Bill <Wehrum.Bill@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Greaves, Holly <greaves.holly@epa.gov>; Ross, David P <ross.davidp@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Bodine, Susan <bodine.susan@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Palich, Christian <palich.christian@epa.gov>; Jackson, Ryan <jackson.ryan@epa.gov>; Wright, Peter <wright.peter@epa.gov>
Cc: Molina, Michael <molina.michael@epa.gov>; Humphreys, Hayly <humphreys.hayly@epa.gov>; Eby, Natasha

<eby.natasha@epa.gov>; Frye, Tony (Robert) <frye.robert@epa.gov>; Shimmin, Kaitlyn <shimmin.kaitlyn@epa.gov>; Block, Molly <block.molly@epa.gov>; Hewitt, James <hewitt.james@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Aaron Ringel (ringel.aaron@epa.gov) <ringel.aaron@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>; Rodrick, Christian <rodrick.christian@epa.gov>; Konkus, John <konkus.john@epa.gov>
Subject: AW Murder Boards
Importance: High

Internal and Deliberative

Colleagues—thank you for all of your efforts in preparing AW for his confirmation hearing. To further prepare him, AW will be subjected to two "murder boards"—one at the White House and one at EPA. In order for this to be successful, I am requesting participation from you and/or senior members of your team. Please let me know ASAP if you are not able to facilitate this request.

Below are the details for next week's murder boards. We will work with the White House to finalize the logistics (WAVES, etc). Due to the shutdown we will need to check our check internal resources to see if we can arrange transportation for the group. Please let me know if you have any questions or wish to discuss further.

JANUARY 14—White House
Time 9:00AM—12:30PM
Location Eisenhower Executive Office, Indian Treaty Room
Format

- Formal murder board—two rounds, 5 minutes per round
- EPA and White House participants
- Participants will not portray specific Senators
- Murder board participants will be expected to ask AW questions relevant to their program offices
- A "feedback" session will be conducted after the Q&A segment has finished

JANUARY 15—EPA
Time 9:00AM—12:00PM
Location EPA, Green Room
Format

- Following a "round robin" format, murder board participants will ask a question or two of AW and then the Q&A will move to the next participant
- Only EPA participants
- Participants will not portray specific Senators
- Murder board participants will be expected to ask AW questions relevant to their program offices.
- Feedback provided on the spot
- Questions should be asked more than once, and in different forms, to help craft the answers

Troy M. Lyons
Associate Administrator
Office of Congressional & Intergovernmental Relations
U.S. Environmental Protection Agency
202-309-2490 (cell)

Message

From: cmsadmin@epa.gov [cmsadmin@epa.gov]
Sent: 8/7/2018 2:26:16 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]
Subject: CMS For Your Information - Maria Carroll - OAR-18-000-9771

Control OAR-18-000-9771 has been forwarded to you on 8/7/18 10:26 AM by Maria Carroll. Please go to the CMS webpage to view the details of the control.

Summary Information -
Control Number: OAR-18-000-9771
Control Subject: Letter regarding results of the Naval Nuclear Propulsion Program's environmental radiological monitoring and of the Program's performance in minimizing pe4rsonnel occupational radiation exposure and disposing of radioactive waste - Report NT-18-1
From: Mueller, T.J.

Note: This Email was automatically generated. Please do not attempt to respond to it. You can access this control at https://cms.epa.gov/cms. Questions or comments concerning CMS should be directed to CMS Support at 202-564-4985 or CMS Information@epa.gov.